MERGE
Myalgic Encephalomyelitis Research Group for Education & Support

Conference Report

American Association for Chronic Fatigue Syndrome (AACFS) 6th International Conference on Chronic Fatigue Syndrome, Fibromyalgia and Related illnesses

Friday 31 January to Sunday 2 February 2003
Chantilly, Virginia (Washington DC)

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STATEMENT: This report is based on the (necessarily imperfect) recollections and notes of Neil Abbot, supplemented by printed information in the conference syllabus. It almost certainly contains errors. Authors of papers at the conference are positively encouraged to bring to the attention of the author (at merge.ncabbot@pkavs.org.uk) errors of fact or opinion where they have occurred. These will be corrected speedily, and the report updated on the website as soon as possible. Also, the contents of the presentations or abstracts, particularly the "Author's Conclusions" sections, do not necessarily reflect the considered opinion of MERGE.

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The financial support of these dedicated organisations enabled Dr Vance Spence to attend and present his scientific work on the biomedical basis of the illness; Dr Gwen Kennedy (MERGE Research Fellow) to give an oral scientific presentation and two poster presentations on her biochemical findings; and Dr Neil Abbot to attend the conference and produce this report.

MERGE
(UK Charity no. SC036942),
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http://www.meresearch.org.uk.
The primary aim of MERGE is to identify, commission and fund scientific investigations into the causes, consequences, and treatment of ME/CFS. It also aims to supply good-quality information, and to facilitate social care provision.

Preface

The AACFS conference of January-February 2003 contained several valuable contributions towards the understanding of ME/CFS. The clinical day - aimed at the education of clinicians - included two useful overviews of the problem (by Drs Jason and Lapp), and several discussions of available treatments for specific symptoms. On the science, the excellent overview of the biochemistry by Dr Suhadolnik explored the biochemical processes that are altered in ME/CFS, while a range of presentations illustrated several aspects of ongoing biomedical investigations. These included the work by Dr Suhadolnik's group at Philadelphia into dysregulation of the 2-5A/RNase L pathway, particularly the potential use of RNase L fragments or their ratios as biomarkers of the illness; the observations by Dr Kennedy (Scotland) and Dr Racciatti (Italy) of increased oxidative stress; the phenomenological reports by Dr Natelson (New Jersey) of spinal fluid abnormalities, and by Dr Spence (Scotland) of abnormalities of acetylcholine clearance in the skin; and the presentations by Dr Behan (Scotland), Dr Gaffney (Minneapolis), and Dr Vernon (Atlanta) describing their results from gene expression profiling.

These studies, and other biomedical investigations in the past two years, illustrate the progress that can be made if researchers have the necessary impetus and funding. With increasing recognition of the limitations of the diagnostic construct "CFS" - exemplified by the recent publication of the new Canadian definition, and the ongoing attempts to improve the sensitivity of the 1994 (Fukuda) definition - and growing international consensus around the need to identify clinically relevant subcategories within it, attention is turning (finally) from the non-curative psychosocial "coping" strategies towards explaining why morbidity is so high for so long in many people with ME/CFS, and uncovering the cause of the illness. As the hoo-ha subsides, the real target comes into view.

Despite these advances, biomedical research into ME/CFS has been meagre, given that its prevalence (somewhere between 200 and 400/100,000 in developed countries) exceeds that of several illnesses which nevertheless have a higher public profile, attracting far more sympathy and resources. The number of poster presentations and oral presentations at the 2003 AACFS conference (44 and 47 respectively, down from 72 and 41 respectively in 2001, and 57 and 46 respectively in 1999) reflect the relatively low level of medical and scientific interest in this illness. There are probably many reasons for this, including the controversial nature of the field, the clinically-diverse nature of the illness, and an intellectual inertia among clinicians and work-a-day scientists. However, the central problem is surely lack of funding, especially over the medium to long term.

In developed societies, class I funding - from national government and central research sources - is scarce, competitively allocated, and subject to many competing priorities. Recent events surrounding ME/CFS funding via the Medical Research Council in UK, and the impending decline in such funding by the NIH in America, have illustrated the difficulties researchers face in obtaining and maintaining class I support. In addition, given the limitation on resources, it is unlikely that "central" funding alone can allocate to ME/CFS research more than a very small portion of a finite cake. For these reasons, there is a growing realisation that for biomedical investigation to prosper, funding will have to come from not-for-profit organisations and charities, such as MERGE, and private benefactors. In effect, the funding strategy for ME/CFS research will have to mirror that of cancer research, which obtains 85-90% of its funds from private sources. A daunting thought. Yet, privately-funded research - bringing fresh ideas and new blood - is commonplace in other chronic illnesses, and ME/CFS need be no different. In truth, there is no alternative if we want biomedical research to move forward (in Churchill's words of 20th August 1940), "in full flood, inexorable, irresistible, benignant, to broader lands and better days".

Neil C. Abbot
March 2003

INTRODUCTION AND OVERVIEW: Charles W. Lapp, MD

The first day of the conference consisted of "clinical" sessions, designed for physicians who wished to learn more about CFS. In his introduction, Charles Lapp discussed the Provider/Education Project and directed the attendees to the self-study course - a web-based study programme containing custom-made information on CFS for clinicians - available at CFIDS: http://www.cfids.org/resources/print-self-study-module.asp; or http://www.cdc.gov/ncidod/diseases/cfs.

LECTURE: Dr Leonard Jason, PhD. Chronic Fatigue Syndrome - The Problem

Dr Leonard Jason gave an overview of CFS. Much of the information contained in this lecture is available at http://condor.depaul.edu/%7Eljason/cfs/. In the presentation, he covered issues surrounding the diagnosis, psychiatric co-morbidity and prevalence of CFS. He described certain myths about CFS, such as the belief (most prevalent in the late 1980s and early 1990s) that patients had "yuppie flu"; that very few members of the minority groups had CFS; and that well-educated women were proportionately over represented in the patient group. These beliefs were erroneous, and emanated from early investigations which were almost certainly unrepresentative of the public as a whole.

He described some of the problems arising from the adoption of the 1994 (Fukuda) criteria for CFS. One major difficulty is that a person with major depressive disorder can be diagnosed as having CFS if they report (a) chronic fatigue and (b) four minor symptoms which can occur with depression, for example unrefreshing sleep, joint pain, muscle pain, and impaired concentration. Importantly, however, he described some of the clear differences which exist between CFS and depression, taking much of this information from the papers by Komaroff et al (Am J Med 1996; 100(1): 56-64 and Am J Med 1996; 101(3) :281-90) in which severe, debilitating fatigue was found to have occurred in 100% and 28% of CFS and depression cases, respectively; acute onset of illness in 84% and 0%, respectively; post exertional malaise in 79-87% and 19% respectively; alcohol intolerance in 60% and 21%, respectively; difficulty initiating asleep in 53% and 26%, respectively; early morning awakening in 19% and 58%, respectively; nausea in 58% and 16%, respectively; and flu-like symptoms in 43-65% and 10-22%, respectively. From these data, it can be seen that the existence of severe debilitating fatigue, an acute onset of illness, post exertional malaise, alcohol intolerance, and a low incidence of early morning awakenings are just some of the elements which separate CFS from the major depressive disorders. Indeed, Dr Jason made it clear that the clinician can differentiate CFS from the major depressive disorder by being cognisant of mode of onset of illness, major symptoms, symptom attributions, fatigue, sleep disorders, post-exertional malaise, cognitive difficulties, psychological symptoms, neuroendocrine problems, patient history, course of illness, and response to treatment. Importantly, he pointed out that when he asks people, "if you were well tomorrow, what would you do", CFS patients generally list a range of activities, whereas patients with clinical depression generally say they do not know. Again, when he asks patients what happens when they push themselves too far, CFS patients generally say that they feel worse, whereas patients with clinical depression say that they feel better.

Coming to the distinction between CFS and generalised anxiety disorder, while these two conditions share some symptoms - such as fatigue, difficulty concentrating, sleep disturbance, irritability, restlessness and rapid heartbeat - they can be differentiated by the most prominent symptoms, chiefly, excessive persistent worry in generalised anxiety disorder, and severe debilitating fatigue in CFS.

CFS can also be distinguished from somatization disorder (SD). The criteria for a diagnosis of SD generally involve the presence of 4 pain symptoms, 2 gastro-intestinal symptoms, one sexual symptom and one pseudo-neurological symptom. However, as Dr Jason notes, the clinical decision about whether to label a patient "CFS" or "SD" involves a large subjective element on the part of the clinician, and can easily be influenced by his/her prior beliefs about the origin of the patients' symptoms. These beliefs can play a large part in how the scoring criteria are used. Indeed, differences in view about illness aetiology may be part of the reason for the acrimonious debate between the proponents of somatization and clinicians who favour a biomedical explanation for CFS. To illustrate the existence of a large subjective element in the diagnosis of SD, Dr Jason described the paper by Deale and Ward (J R Soc Med 2000; 93(6): 310-2) concerning the accuracy of physician diagnosis. Of sixty-eight people with CFS, 31 had been given a psychiatric diagnosis but 68% of these diagnoses proved to be incorrect, while in the remaining 37 patients (who had not been given a psychiatric diagnosis), 35% were found to have a treatable psychiatric condition. These results suggest a "breakdown" in the diagnostic process: it may be that the professionals supplying incorrect diagnoses are following their own biases regarding the aetiology of the patient's illness rather than looking objectively at the clinical picture.

Dr Jason suggested three observations which may help to differentiate CFS from SD. First, fatigue is the *primary* feature of the illness in CFS, whereas it is not necessarily so in SD. Second, CFS generally has a sudden onset symptom complex in the 30s or 40s age group, unlike SD. Third, symptoms of SD - but not CFS - escalate over several years to full-blown disorder, generally by the age of 25. Dr Jason considers it vital

that in complicated clinical cases, such as most CFS patients, there should be a multi-disciplinary assessment from a range of specialists, not just input from psychiatric professionals.

Coming to the issue of fatigue *per se*, fatigue is relatively common in populations; the proportion of patients attending primary care with prolonged fatigue is approx. 15-30%; and the proportion with chronic fatigue, i.e. of greater than 6 months duration, is approx. 10-20% (*vide* the review by Lloyd AR. Am J Med. 1998; 105(3A): 7S-10S). In the population of the USA, it is estimated that a quarter of the population report general fatigue, when asked about it on any one day; 7% (14 million people) report prolonged fatigue, when asked about fatigue over the past month; and some 4% (8 million people) report chronic fatigue, lasting for 6 months or more. CFS itself is estimated to affect over 800,000 adults and adolescents in the USA, confounding the myth that CFS is a relatively rare disorder (Jason et al. Arch Intern Med 1999; 159(18): 2129-37). Nor is CFS confined to young, affluent, white professionals: Latinos have a prevalence rate of 726 per 100,000; Whites, 318 per 100,000; and African/Americans, 337 per 100,000, as determined by this population-based community sample. The reason for the racial differences are unclear, but there have been suggestions that many affluent whites are on a low-salt diet (related to orthostatic hypotension) or that the non-white racial groups are more likely to be on Medicare, leading to the under-diagnosis of CFS. Interestingly, these racial differences - found in a population-based sample - are not apparent within the case-loads of most physicians in the USA, and it may be that under-diagnosis is widespread among the more disadvantaged members of society.

From the same population sample, women were found to have a much higher rate of CFS than men (522 women versus 291 men per 100,000). This figure for women - 522 per 100,000 - represents a prevalence of CFS in the USA higher than for some other, more well publicised, disorders, such as women with HIV (125 per 100,000), women with lung cancer (43 per 100,000), women with breast cancer (26 per 100,000). However, given this apparent prevalence of CFS in the USA, the funds available for research and treatment are rudimentary compared with what is available to the other major disorders. While $1.8 billion was spent on AIDS in 1997, $409 million on breast cancer in 1997, and $315 million on Alzheimer's Disease in 1997, in the ten years from 1987-97 only $100 million in total was spent on the research and diagnosis of CFS. Dr Jason also pointed out that there is evidence that people with CFS have higher levels of functional impairment than those suffering from a type 2 diabetes mellitus, congestive heart failure, multiple sclerosis and end-stage renal disease. (e.g., Anderson et al. J Nerv Ment Dis 1997; 185(6): 359-7). As regards prognosis, while many patients show improvement over 2 years, the majority remain significantly impaired.

As regards childhood sexual or physical abuse, most respondents with CFS did not have a history of either or both of these. In fact, 16% had a history of childhood sexual abuse, 29% of childhood physical abuse and only 6.5% had a death threat in childhood. Again, looking at the family history of illness in people with CFS, there seemed to be a higher prevalence of auto-immune diseases in CFS (50%) than in a control group (28%).

Central to any discussion of CFS are the problems related to the 1994 (Fukuda) definition of CFS. There are many sources of ambiguity in the definition, e.g., the meaning of "persistent or relapsing chronic fatigue" or "new or definite onset", the fact that symptoms can be either present or absent without consideration of their severity, and the definition of post-exertional malaise lasting more than 24 hours. The results of the review of the 1994 definition to be published in 2003 may help to resolve some of these difficulties.

The measurement of CFS definitional symptoms is extremely complex. As regards the major symptom - fatigue - accurate measurement crucial. In a review of fatigue scales (Taylor et al. Psychol Med 2000; 30(4): 849-56), the Krupp fatigue severity scale (Krupp et al. Arch Neurol 1989; 46(10): 1121-3) was found to be preferable, and appeared more sensitive than the Chalder scale, at least for fatigue. Interestingly, this study indicated that people with CFS scored significantly higher than those with MS or depression on the Krupp scale. In practice, the two scales most commonly used to measure substantial reductions in daily activities are the Sickness Impact Profile and the Medical Outcomes Scale (SF36).

For the measurement of depression at the point of diagnosis, the Beck depression inventory is commonly used. Dr Jason reported that in one PhD thesis (Carolyn King, DePaul University) the items concerned with self-reproach were found to be lower in people with CFS than in people with depression, possibly providing a good marker for differentiating these groups. For the measurement of psychiatric co-morbidity, Dr Jason and colleagues prefer the Structured Clinical Interview (SCID), seen as preferable to the Diagnostic Interval Schedule.

Future refinements of the diagnostic criteria for CFS may require measurement of the *severity* of symptoms: for example, a 4-item scale could contain categories from full remission (no longer any symptoms) through partial remission (full criteria for the disorder were previously met but currently only some symptoms exist) and moderate (few symptoms in excess of those needed for the diagnosis are present) to severe (many symptoms in excess of those needed for the diagnosis are present).

The minor CFS definitional symptoms are cognitive symptoms, tender neck/lymph nodes, muscle pain, multi-joint pain, sore throat, headaches, unrefreshing sleep, and post-exertional malaise. It is important to realise that healthy people can have 4 or more of these symptoms, but that in people with CFS the symptoms tend to be much more intense, and are "score" at a much higher level than in the control subjects. So, in future revisions of the CFS criteria, it may be wise to assess the intensity of a particular symptom. With the minor criteria symptoms, the mode of questioning is important. When enquiring about unrefreshing sleep, the clinician - rather than asking, “Is sleep unrefreshing, yes or no?" - is advised to ask, “Did the patient awake tired or unrefreshed?”, and to classify the response a 4 point scale - never, seldom, often or usually, or always. This has been found to be a useful adjunct for the differentiation of people with CFS from other kinds of patients.

In recent years, actigraphs (kept on the patient’s wrist to indicate activity over a 24-hour period) have come to be used by some clinicians and their researchers as a way of estimating the activity. In healthy people, there are high peaks during the day which fall to virtually no activity at night, whereas in people with CFS there are no or very few high peaks during the day and signs of restlessness during the night, indicating a lack of restorative sleep. In future, these devices may come to be useful aids in the diagnosis of CFS.

LECTURE: Charles W Lapp, MD. Chronic Fatigue Syndrome - A Diagnostic and Management Challenge

Dr Lapp briefly sketched the history of CFS and pointed out that the modern illness CFS is characterised by fatigue which interferes with daily activities, which has lasted greater than 6 months, which is accompanied by flu-like symptoms (muscle and joint pain, sore throat and headaches), by cognitive complaints such as confusion, and by disorders of sleep.

As recently highlighted in the Canadian Clinical Working Case Definition Report (Carruthers BM et al. Journal of Chronic Fatigue Syndrome 2003; 11(1): 7-115), sleep disorders can be very distinctive in CFS, involving *non-restorative* sleep, *difficulty initiating/maintaining* sleep, and possibly dysania (morning foggy-headedness). He stressed that, in the absence of diagnostic markers, we must rely on the 1994 (Fukuda) case definition which was, nevertheless, created for research purposes.

Dr Lapp discussed the following points concerning CFS-definitional fatigue: (a) that it is medically unexplained, other explanations for fatigue having been ruled out; (b) that it is of new onset (i.e. not lifelong, a fact which could indicate a depressive condition); (c) that it is of at least 6 moths duration (a timescale arbitrarily chosen because many patients do, in fact, present with flu-like illnesses lasting from 1-6 months which resolve with time); (d) that it is not the result of on-going exertion (since there are specific fatiguing illnesses caused by muscle over-exertion); (e) that it is not substantially relieved by rest, implying that there is a ceiling on the amount of work that a person can do; and (f) that it causes a substantial reduction in previous levels of occupational, educational, social or personal activities.

As regards the 8 minor criteria described above - 4 or more of which must be present for the diagnosis to be confirmed - it is important to note that these symptoms should not be used as a simple "check-list". Many healthy people will also report some of these, and each symptom must be evaluated by the clinician keeping CFS in mind. These consist of impaired memory or concentration (which can be substantially impaired in CFS); sore throat (which is most often frequent or persistent); tender cervical or axillary lymph nodes (usually cervical chain but persistent/recurrent); muscle pain (myalgia); headaches of a new type, pattern, or severity which have developed since the onset of the illness (typically, these headaches are of the pressure type); unrefreshing sleep (non-restorative or difficulty initiating/maintaining sleep as above); multi-joint pain without swelling or redness (most often an ache or a throbbing flu-like illness or deep bone pain); and post-exertional malaise which may be the most specific symptom for CFS – there are few, if any, other diseases in which this is a prominent symptom.

It is important for the clinician to recognise the exclusionary conditions. These include (a) active medical conditions known to cause fatigue; (b) significant psychiatric disorders (e.g., melancholic or psychotic depression, bi-polar affective disorder, schizophrenia or psychosis, dementia, or eating disorders); (c) alcohol or substance abuse (which is the principal cause of depression); and (d) morbid obesity (BMI > 40 or 45).

At physical examination of a CFS patient, the findings are most typically normal but there may be low-grade fever, low blood pressure, lymphadenopathy, allodynia (pain from stimuli which are not normally painful, or occurring in areas other than in the area stimulated) and tender points. Interestingly, allodynia is relatively common in CFS. As regards laboratory findings in CFS, most of these are only suggestive - they are not specific for the disorder and, indeed, are typically normal except for immune complexes, atypical lymph nodes, increased alkaline phosphatase, reduced IgG, increased cholesterol levels and the presence of autoantibodies. Looking at brain imaging techniques, MRI studies have shown high intensity T2-weighted lesions usually over the cerebral convexities. These are also called UBOs (unidentified brain objects) but they are also seen in other conditions, for example, Sjogren’s disease and Lyme disease, and appear not to be

diagnostic for CFS. SPECT studies of the brain have appeared to demonstrate reduced cerebral blood flow in the temporal lobes and the mid-brain after exertion but, again, these observations have been made in other disorders and are supportive for the diagnosis of CFS but are not diagnostic *per se*.

There is some evidence that precipitating factors are important in CFS: in one study (Salit IE. J Psychiatr Res 1997; 31(1): 59-65) only 15% of people with CFS reported that their illness began insidiously. Of those identifying a precipitating factor, bacterial or viral infection occurred in 72%, trauma in 4.5%, surgery or childbirth in 4.5%, allergic reaction in 2.2%, and stress/emotional trauma in 1.7%. Dr Lapp confirmed that - anecdotally - most people with CFS can say to the day when they fell ill, and that this fact can itself be an indicator of the diagnosis of CFS. As an aside, Dr Lapp pointed out that it is difficult to diagnose CFS in children less than 4 or 5 years old since school reports are often important for diagnosis.

There are numerous theories about the possible causes of CFS. These include infectious agents, immunological deficits, hypothalamic-pituitary-adrenal axis dysfunction, and orthostatic intolerance. On orthostatic intolerance, many clinicians have noticed that it seems to be a prominent feature of people with CFS and that the tilt-table test is positive in a large number; indeed, Dr Lapp reported that more than half of all CFS patients have significant levels of orthostatic intolerance. This raises the question of whether orthostatic intolerance is a cause of the illness, preceding the development of CFS for years, though it is not possible to verify this at present. Interestingly, whereas individuals with, for example, diabetes have an immediate orthostatic intolerance reaction to a tilt-table test, in CFS this seems to be delayed for 10-15 minutes, and it is therefore important to keep people with suspected CFS standing up for 15 minutes after the tilt-table test before measuring orthostatic intolerance.

Thus, looking at the CFS diagnostic decision-making model, a patient should have had chronic or relapsing fatigue, for more than 6 months (but not lifelong), that should significantly affect lifestyle or ability to work, and that should be unexplained by other exclusionary tests and medical conditions including neurological, psychiatric evaluation. In addition, the patient should have 4 or more of the 8 minor symptoms detailed in the 1994 definition. Elements of the initial laboratory work are listed at http://www.cdc.gov/ncidod/diseases/cfs/defined/defined5.htm, but they should include urinalysis, a complete blood count with differential thyroid function tests and a chemistry panel, albumin/globulin, SGOT/SGPT, alkaline phosphatase, calcium phosphorous and a glucose tolerance test. If another plausible explanation for the symptoms is found from these tests then CFS can be excluded as a diagnosis. The range of differential or alternative diagnoses that could explain CFS come under a variety of headings, such as infectious diseases - whether viral (e.g., herpes virus), bacterial (e.g., Lyme Disease), parasitic (e.g., Toxoplasma) or fungal (e.g., Coccidiomycosis); neuromuscular diseases (e.g., multiple sclerosis and myasthenia gravis); the autoimmune disorders (e.g., systemic lupus and vasculitis); the endocrine disorders; adverse affects of drug medications; psychiatric conditions; and the conditions associated with malignancy.

Considering conditions that appear to overlap with CFS in some studies, Fibromyalgia requires widespread pain for at least 3 months and at least 11 of 18 classic tender points (1990 American College of Rheumatology Criteria). Also, Gulf War illness shares some symptoms in common with CFS, though one study (Steele et al, Am J Epidemiol 2000; 152(10): 992-1002) indicated that of 1548 veterans, 7% had clinically definable CFS. Multiple chemical sensitivities (MCS) are also thought to overlap with CFS, and symptoms include cognitive impairment, mood disorder, headaches and fatigue. However, the consensus definition of MCS (Arch Environ Health 1999; 54(3): 147-9) indicates, among other things, that symptoms should be reproducible with repeated chemical exposure and that symptoms should improve or resolve when the chemical agents are removed. Comparing patients with CFS, Fibromyalgia and MCS (Buchwald and Garrity, Arch Intern Med. 1994; 154(18): 2049-53), it was found that patients with CFS frequently report MCS and that some 30% of MCS patients also meet the criteria for CFS.

LECTURE: Charles W. Lapp, MD. Drug Treatment Strategies

This presentation described a step-wise approach to the management of CFS, represented by an ascending staircase with 4 steps: education, activity, nutrition/vitamin supplements and specific therapies.

The first of the steps towards effective management of CFS is *education*, involving reassuring the patient that his/her illness is real, initiating pathophysiological investigations, sketching the possible prognosis in the medium to long-term, and suggesting some coping strategies that could be used. In the second step, *activity*, suggestions are given that strict bed rest should be avoided, and that light activity should be balanced with frequent rest and a gentle programme of modalities, such as stretching, light weights, low-level interval exercise (5 minutes on and off). It was emphasised that although may clinicians have heard that graded exercise can be helpful, patients should not embark on an exercise regime which increases the severity of illness, a phenomenon occurs, as many experienced clinicians recognise, when patients push themselves too much. *Nutrition* involves a prudent diet (low fat, including fresh vegetables and pasta, and the avoidance of functional malnutrition), the minimisation

of SCAT (Sugar, Caffeine, Alcohol, Tobacco), and the avoidance of chronic diarrhoea (implying the avoidance of dairy products, gluten, etc.).

At the fourth step, *specific symptomatic therapies*, the physician can recommend specific therapies that help with sleep management, central activation (fatigue and cognition), the disautonomias, and the management of pain. For sleep management, the following options could be used: (a) melatonin phototherapy; (b) over-the-counter medications; (c) clonazepam at a very low dose, 0.5 mg, mindful of the possibility of habituation, and doxepin, 10 mg. Trazadone, 50 mg, or some of the hypnotics can also be used in the attempt to increase stage 3 and 4 sleep. As regards central activation therapies for the treatment of fatigue and cognitive difficulties, it is known that reduced levels serotonin or dopamine can lead to (a) sleep disturbance, (b) low-pain threshold, (c) lack of motivation, and (d) depressed mood. Therefore, SSRIs, such as fluoxetine or sertraline, can be used, bearing in mind that these are not necessarily used because of depressed *per se* but rather to attempt to raise serotonin levels. SNRIs, such as venlafaxine and the dopominagonists, can also be used. Regarding autonomic nervous system dysfunction, treatments can include volume expansion with salt and water (consisting of drinking at least 2 quarts of fluid per day supplemented by appropriate quantities of salt), and fludrocortizone, 0.1-0.3 mg/day. Beta blockers may be useful as some patients may benefit from a rise in blood pressure, and vasoconstrictors, e.g., ephedrine, can be prescribed.

LECTURE: Dr Benjamin Natelson, MD. Drug Treatment Strategies

Dr Natelson reviewed his personal approach to pain control. He stressed that much of his use of specific therapies was empirical since the evidence-base for their use was not highly developed. However, satisfactory management of pain on its own can dramatically improve the quality of life in people with CFS, and the issue is an important one. Stage 1 of a pain management strategy could consist of non-steroidal anti-inflammatory drugs, e.g., celebrex 200 mg BID, though there is scant evidence that they are effective for pain; tricyclic anti-depressants, though these are associated with weight change, complicating compliance; and amitriptyline at a very low dose could be used if disturbance of sleep is a problem. At this stage, the mixed anti-depressant venlafaxine may also be useful. Stage 2 of a pain management programme could involve anti-epileptic drugs, which are still mostly used for the painful neuropathies, especially diabetic neuropathy. It is possible to start with gabapentin, sequentially increasing the dose up to 3 g/day if this is helpful, but if this is not well-tolerated lamofrogine can be used. It may be necessary to go up to trileptal and topamax, though the latter may aggravate problems with cognitive function. Stage 3 could involve tramadol, up to 15 mg QID; tizanidine, up to 100 mg TD; or lidocaine patches for local pain. Phase 4 includes the opiates, though not for prolonged periods of time. These include methadone which, though cheap, has a long half-life, and morphine sulphate up to 300 mg BID.

Presentations on non-pharmacological treatments

- **Patricia A Fennell, MSW** gave a presentation on the application of her four-phase theory of chronic illness populations to people with CFS for whom the experience of chronicity is very real, and who require assistance to cope. Four-phase theory attempts to describe four phases of traumatic and chronic change in response to a chronic illness. The model attempts to characterise the three domains of patient experience at each phase namely, physical behaviour, psychological, and "social interactive". Phase 1 represents the trauma/crisis phase undergone when coping with the effects of a new illness, and may include elements such as loss of psychological control, despair, isolation and mood swings, and social interactive difficulties. Phase 2 is the stabilisation phase during which the patient can carve ordered chaos, resulting, possibly, in stabilisation of some symptoms. In phase 3 - which is the resolution phase - the patient works towards developing meaning and accepting the ambiguity and chronicity of chronic illness. In Phase 4, the patient integrates chronic illness and pre-and post-illness self-concepts. The usefulness of viewing illness in terms of the these phase models lies in the potential to measure, by means of the standardised questionnaire, qualitative differences in patients as they progress through the phases, and in the need to understand patients' experiences separately as a function of the particular phase of the illness. Studies have been conducted to validate this phase model on CFS patients (e.g., Jason et al. J Clin Psychol 2000; 56(12): 1497-508).

- ***Donald Uslan, MA, MBA,*** working in private practice, described the use of a memory/cognitive work-book, essentially a means of promoting self-management of CFS. He pointed out that many patients become bound up in their illness and symptoms, and by their relationships with doctors. Problems with sleep are the most harrowing symptoms for patients, and two particular aspects may increase the problem: information overload (excessive thinking), and lack of sleep hygiene. Self-management of the illness should include practical ways of preparing for the sleep experience.

- ***Dr Stanley Schwartz, MD*** described the practical management of people with CFS, the aim being to improve energy, improve cognitive function (for example, by using cue cards, reducing ambient noise, etc.), optimise pain control, increase their acceptance

and understanding of illness, and - importantly - improve sleep using a variety of helpful interventions. Since it is estimated that 40-50% of people with CFS become chronically disabled, it is important that this is prevented if possible. In patients, the chief complaint is usually the number of symptoms, and specific data collection forms are needed to understand these. It is necessary to evaluate the impact of symptoms as well as the symptoms *per se*, so instruments which can sensitively measure symptoms and their impact are required. It is important for the clinician to allow adequate time for the patient's reports to be heard and dealt with. The role of support groups was briefly discussed: these are patient-led rather than profession-led and Dr Schwartz commented that these may, in some cases, serve to reinforce the experience of illness. Physicians cannot be "islands of care", however: they need to be one among a "network" of care practitioners, albeit that building up and retaining such a team can be very difficult. In this way a "team memory" can be developed, and patient care provided over a range of domains. These teams can consist of a nurse medical assistant, a rehabilitation professional, and a psychosocial support worker. Dr Schwartz also highlighted the most devastating 3 "Ds" which can befall individuals with CFS, namely, Divorce, Destitution and Disability. As regards the network of care, he stressed that family input is very important. In addition, vocational rehabilitation (and related aspects, such as disability issues, work-place adaptations and the requirements of the Americans with Disabilities Act) should be considered. In his own practice, Dr Schwartz has a "patient and families symposium" once a year at which issues can be discussed.

LECTURE: Charles W Lapp, MD. Disability and Prognosis

Given the level of disability seen in the over 800,000 people with CFS, and the more than 2 million people with Fibromyalgia, primary care physicians have a daunting task. Social Security evaluation is often required since both CFS and Fibromyalgia can result in substantial disability. Some 14% to 51% of people with CFS are unable to work, and from 1989-93, for example, disability applications increased by 360 to 560%. Ideally, for the effective evaluation of impairment in CFS, the primary care evaluator should be familiar with the illness, standard criteria should be met, and other plausible causes excluded. Patients should receive psychometric and physiological testing, and the results should be professionally evaluated. The presentation discussed the use of standardised psychometric instruments, such as the Hamilton Depression Scale and the Fatigue Impact Scale, and the role of functional capacity testing. It was stressed that physical therapy evaluation was often unsatisfactory in CFS patients since it did not take delayed symptoms into account. However, functional capacity evaluation can be useful, and techniques include cardio-pulmonary exercise testing using a bike ergometer and expired gas analysis. These techniques can confirm impairment, quantify severity, and controls can be employed to validate the results. Importantly, these tests are acceptable for the Social Security system in USA.

As regards Social Security Disability evaluation, the SSA poses three medical questions with respect to disability: (a) is there a medically determinable impairment; (b) does the impairment limit the ability to perform substantial gainful work; and (c) is the impairment expected to last for a continuous period of at least 12 months (or result in death). To establish a medical determinable impairment in people with CFS (Social Security regulation 99-2P), and prove the presence of CFS to the SSA, it is important that the patient meet the 1994 CDC case definition criteria for CFS, have one or more specific medical *signs*, clinically documented over at least 6 consecutive months (e.g., swollen or tender lymph nodes, non-exudative pharyngitis, persistent muscle tenderness on examination, and any other medical signs). It also helps if there are specific laboratory findings (such as elevated EBV, abnormal cranial MRI , NMH by tilt-table testing), and any other lab findings determined from cardio-pulmonary exercise testing etc., or sleep apnoea. Again, ongoing cognitive deficits could include short-term memory problems, problems with information processing, concentration, speech, word-finding, or calculation difficulties, as well as problems with anxiety or depression. As an aside, Dr Lapp mentioned anecdotal reports from the USA that CFS and Fibromyalgia are now being classed as exclusions for some insurance policies.

LECTURE: Leonard A. Jason, PhD: Prevalence Rates of Medically Unexplained Illness

This presentation included information which can be found at Dr Jason's instructive departmental website (http://condor.depaul.edu/%7Eljason/cfs/CFSepidemiology.htm). In brief, fatigue is a common symptom in primary care: approx. 4% of patients (8 million adults in the USA) were found to have chronic fatigue (Jason et al. Arch Intern Med 1999; 159(18): 2129-37). As regards Fibromyalgia, the review by Wolfe et al. (Rheum Dis Clin North Am. 1990; 16(3): 681-98) found rates to be 3.4% in American women and 0.5% in American men. Looking at Gulf War Syndrome, Kang et al (J Occup Environ Med 2000; 42(5): 491-501) in a population-based study of 15,000 Gulf War veterans and controls found 5.1 % of Gulf War veterans met the criteria for CFS. The conclusion from these figures is that the population rates of these "medically unexplained illnesses", as they are coming to be called, are quite substantial. As regards the 4% of individuals with Chronic Fatigue, the current estimate is something like

one tenth of these (i.e. 0.4% of the population of the USA) fulfil the criteria for CFS. However, estimates of prevalence have varied widely between studies: Price et al (1982) found a figure of 7.4/100,000; Rayes et al 1997, 8.7/100,000; Lloyd et al 1990, 39.6/100,000; Rayes et al 1998, 183/100,000; Jason et al 1995, 200/100,000; Buchwald et al 1995, 267/100,000; Lawrie et al 1997, 740/100,000; and Wessley et al 1997, 2600/100,000. The reasons for these discrepancies are that different studies use different criteria for diagnosing CFS, and also that there are methodological differences between studies. That the criteria for measuring CFS is important, can be seen from the fact that when the 1994 definition of CFS is compared with the recent Canadian Case Definition, it is apparent that the Canadian criteria select cases with (a) less psychiatric co-morbidity (b) more physical functional impairment and (c) more fatigue/weakness, neuro-psychiatric and neurologic symptoms. Dr Jason mentioned recent attempts to revise the 1994 criteria and referred the conference to the paper by William Reeves which was to give a basic overview of forthcoming recommendations from the International CFS Study Group set up to improve case ascertainment.

One of the methodological problems involved in estimating the incidence of CFS concerns the fact that some patients with CFS are not currently within the traditional health care system and consequently do not have a physician. In addition, some physicians do not believe CFS to be a real clinical entity, and therefore do not diagnose it or refer patients to studies. As regards methodology, a community-based sample is optimum, involving a multi-disciplinary team of physicians, epidemiologists, survey researchers, bio-statisticians, and psychologists. Dr Jason described the initial basic work performed when designing his own community-based sample, including attempts at validation screening. Looking at the study itself (Jason et al. Arch Intern Med 1999; 159(18): 2129-37), stage 1 involved a stratified random sample of households which were screened for symptoms of CFS in a telephone survey. At stage 2, participants with chronic fatigue and a sample of healthy controls completed physical and psychiatric examination to rule out exclusionary conditions, and an independent physician review panel verified CFS cases by a consensus. Looking at the CFS prevalence rates per 100,000, Latinos were found to have the highest rates (726), followed by Afro-Americans (337) and whites (318). The rates were also higher among skilled workers (701) than among unskilled workers (436) or professionals (325), indicating that the term "yuppie flu" was inappropriate. Rates amongst females (522) were higher than amongst males (291). Dr Jason also discussed CFS paediatric prevalence rates (60/100,000) compared with 420/100,000 in adults. No cases of CFS were found amongst children aged 5-12. Interestingly, from a sample of 3,400 nurses (Jason et al. Am J Med 1998; 105(3A): 91S-93S), those meeting the 1994 criteria represented 1088/100,00, i.e. twice the rate in the general population, indicating that health care workers may be at a higher risk of developing CFS.

Presentations on Epidemiology

Sleep Disorders in Population-Based Study of Fatiguing Illnesses Elizabeth R. Unger et al. Centres for Disease Control and Prevention, Atlanta, GA. Dr Unger described how unrefreshing sleep, or failure to initiate sleep, were prevalent among people with CFS, and that their presence was one of its defining symptoms. The aim of the presentation was to describe sleep abnormalities, identified from the 17-item Sleep Assessment Questionnaire (SAQ©), and to determine the association between these disorders and fatiguing illness subgroups. The total study population was 339 subjects, and relevant fatigue subgroups included 41 (12.1%) never fatigued; 145 (42.8%) medical or psychiatric exclusions; 18 (5.3%) CFS at baseline but not meeting criteria after 12 months; and 24 (7.1%) CFS. Sleep abnormalities were significantly more likely among subjects who had ever been fatigued at baseline or at the 12-month point compared with those who remained non-fatigued throughout the 12-month follow-up. In subjects with CFS (n=24) and never-fatigued subjects (n=41), the percentages with non-restorative sleep were 62.5% and 2.4% respectively; with sleep apnoea, 21.7% and 12.2% respectively: with excessive daytime sleepiness, 37.5% and 17.7% respectively; with restlessness, 66.7% and 9.8% respectively; and insomnia, 33.3% and 0% respectively. Clearly, the relationship of sleep disorders to chronic fatigue requires additional study. AUTHORS' CONCLUSION: The relationship of sleep disorders to chronic fatigue requires additional study. The SAQ© is easily incorporated into epidemiological studies and will facilitate studies of sleep pathology and the etiology of CFS. Findings of the SAQ© will need to be validated with formal sleep testing.

CFS Research Case Definition: Lessons Learned 1994-2002 William Reeves, for the International CFS Study Group, Division of Viral and Rickettsial Diseases, National Centre for Infectious Diseases, CDC, Atlanta, GA 30333. Dr Reeves reported on the progress, over the past 3 years, of the International CFS Study Group convened by the CDC to identify ambiguities in the current 1994 CFS research case definition and to make recommendations to improve the precision of case ascertainment. The minutes of these meetings are given in full at the CDC website (CFS section) http://www.cdc.gov/ncidod/diseases/ cfs. He reviewed some of the Group's recommendations, due to be published in full during 2003. These recommendations will include suggestions to further clarify medical and psychiatric exclusions: indeed, exclusions will now be permanent or temporary. For example, a lifetime

diagnosis of psychiatric disorder would still be grounds for exclusion from the definition. However, the presence of certain specific psychiatric disorders will not be considered exclusionary if they have not been present in the 5 years preceding the onset of CFS. Again, conditions causing temporary exclusion until specific treatment is supplied may include hypothyroidism, disorders of sleep and morbid obesity. It will also be recommended that the "somatic syndromes" be a defined subgroup within the larger diagnostic category. As regards ambiguities in the current 1994 CFS research case definition, the "substantial limitation on activity" (caused by fatigue) will be more closely defined. The Group will recommend that the case definition be tested empirically across regions and different cultures, using specific outcome measures and assessment instruments recommended by the group to assess disability and case-defining symptoms. These include standardised outcome measures, such as the Structured Clinical Interview for DSM III R (SCID) for psychiatric assessment; the SIP (Sickness Impact Profile); the Krupp fatigue severity scale; the McGill Pain Questionnaire; and the MOS-SF36 quality of life instrument. Importantly, the group will recommend that published studies should include clear details of the CFS case definition used, and utilise the recommended validated assessment instruments. AUTHORS' CONCLUSION: The Group offers suggestions to further clarify permanent medical and temporary medical and psychiatric exclusions. The Group recommends that the case definition be tested empirically across regions and different cultures by using the instruments recommended.

The Epidemiology of CFS and Self Reported "ME" in 5-15-year-olds Trudie Chalder et al. Academic Department of Psychological Medicine & Department of Health Services Research, Guy's, King's and St Thomas' School of Medicine, London. Dr Chalder described her attempts to determine the prevalence of operationally defined Chronic Fatigue Syndrome and ME in 5 to 15-year-olds, and to examine associations with psychological disorders. This study was part of a larger investigation sponsored by the Office of National Statistics for Scotland, England and Wales. In total 14,250 families were contacted and 10,438 were included. The random sample under discussion consisted of 4,240 11-15-year-olds living in private households. Children were assessed using structured interviews, supplemented by open ended questions, to ascertain whether and to what extent fatigue and psychological disorders were a problem. Parents were asked whether they believed their child had Chronic Fatigue Syndrome or M.E. The main outcomes were fatigue, chronic fatigue and Chronic Fatigue Syndrome operationally defined. Overall, 1,354 (32%) said that they were currently tired. Of these 24 (0.6%) were chronically fatigued and 8 (0.19%) met criteria for Chronic Fatigue Syndrome. Four (0.04%) out of 10,438 parents said their child had M.E. or Chronic Fatigue Syndrome. There was no overlap between children's symptoms and parental labelling. Anxiety and depression were associated with tiredness, chronic fatigue and operationally defined Chronic Fatigue Syndrome in the child. Dr Chalder concluded that CFS rates (equivalent to 189 per 100,000) are comparable with rates of diabetes in this age group, that there was a considerable overlap between fatigue and psychological disorders, and that there was frequent maternal neuroticism. AUTHORS' CONCLUSION: Both operationally defined Chronic Fatigue Syndrome and M.E. are rare in this age group. Operationally defined Chronic Fatigue Syndrome and psychological disorder are treatable.

• ***Physical Impairment in the Chronic Fatigue Syndrome: A Test of the Fatigue Severity Hypotheses*** Kim Busichio et al. Departments of Psychiatry and Neuroscience, UMDNJ-New Jersey Medical School, Newark NJ, USA. Dr Busichio reported that people with CFS have substantial impairment of their ability to perform routine domestic and work-related tasks. This impairment may be due to fatigue or to other symptoms: in particular, pain may be more salient than fatigue in CFS patients with comorbid Fibromyalgia. To explore this, the authors investigated a study sample consisting of 102 females with confirmed CFS attending a tertiary medical centre. CFS and FM were diagnosed by physical examination. A psychiatric interview (DIS) was performed to rule out psychiatric exclusions. Each participant completed an assessment protocol consisting of: SF-36; MFI; and SCL-90. Data were explored using regression analysis to estimate the amount of variance in physical impairment associated with each symptom. Fatigue was only modestly associated with physical functioning and work-related impairment in people with CFS alone (range of R^2 was 1%-7%). Pain was a better predictor of work impairment than fatigue in people with CFS, and people with CFS plus Fibromyalgia. AUTHORS' CONCLUSION: The hypothesis that fatigue accounts for substantial physical impairment in CFS was not supported. Pain may be more of a limiting factor than fatigue in CFS patients with chronic work impairment

LECTURE: Robert J. Suhadolnik, Ph.D. The Biochemistry and Genetics of Chronic Fatigue Syndrome

Dr Suhadolnik listed the biochemical processes that have been found to be altered in CFS: (a) oxidative stress (nitric oxide/peroxynitrite); (b) 2-5A synthetase/RNase L; (c) p68 kinase (PKR); (d) apoptosis (programmed cell death); (e) skeletal muscle function; (f) mitochondrial function; and (g) brain metabolism. In addition, there could be (h) a genetic predisposition.

Describing the peroxynitrite model of CFS (*vide* Pall ML. Med Hypotheses 2000; 54(1): 115-25), Dr Suhadolnik explained that this postulates that infection with a virus or other antigen induces elevated levels of IL-1, IL-6, TNF alpha and IFN gamma. This leads to INOS induction and nitric oxide elevation, leading to peroxynitrite elevation and on to mitrochondrial dysfunction, lipid peroxidation, CA^{++} elevation, and to other damage. HPA, and other organ dysfunction, can ensue, as well as fatigue and other symptoms. This model is supported by the presentation at the AACFS conference of two papers (by Dr Racciatti [Italy] and Dr Gwen Kennedy [Scotland]) indicating oxidative stress in people with CFS.

Looking at the 2-5A synthetase/RNase L pathway (*vide* Suhadolnik RJ et al. Clin Infect Dis 1994; 18 Suppl 1: S96-104, and Shetzline SE et al. J Interferon Cytokine Res 2002; 22(4): 443-56), it has been shown that this anti-viral pathway is upregulated in CFS. This activation of 2-50AS, elevation of bio-active 2-5A, and activation of RNase L leads to the degradation of RNA and inhibition of protein synthesis.

With reference to p68 kinase (PKR), there is evidence that in CFS, PKR mRNA expression and protein activity are increased (*vide* Vojdani and Lapp. Immunopharmacol Immunotoxicol 1999; 21(2): 175-202). Overall, activated PKR decreases protein synthesis, increases apoptosis, increases nitric oxide and peroxynitrite and increases the propensity to allergy. These events can affect a range of physiological processes (Englebienne and DeMeirleir. *Chronic Fatigue Syndrome: A Biological Approach* 2002; pp153).

Increased apoptosis (programmed cell death) has been noted in CFS (e.g., Hassan IS et al. Clin Immunol Immunopathol 1998; 87(1): 60-7, and Vojdani A et al. J Intern Med 1997; 242(6): 465-78). Dr Suhadolnik noted that apoptosis is a complex cellular process which occurs by three mechanisms: (a) release of mitochondrial cytochrome C and caspase 9; (b) trans-membrane death receptors (caspases 3 and 8); and (c) the ER pathway (caspase 12).

As regards impairments of skeletal muscle metabolism in CFS, the paper by Wong R et al. (Chest 1992; 102(6): 1716-22) indicated that CFS patients reach exhaustion more rapidly than normal subjects, at which point they also have reduced intra-cellular concentrations of ATP, suggesting a defect of oxidative metabolism. Again, there are indications that G-actin is cleaved in CFS PBMC extracts (e.g., Roelens et al. JCFS 2001; 8: 63); that there is reduced oxidative muscle metabolism in CFS (McCully et al. Muscle Nerve 1996; 19(5): 621-5) and that muscle oxygen recovery in CFS is delayed compared with control subjects. Interestingly, elevated levels of RNase L are associated with a reduced VO2 max and exercise duration in patients with CFS (*vide* Snell et al. In Vivo 2002; 16(2): 107-9).

Dr Suhadolnik described the evidence for defects in brain metabolism. One recent report (Kuratsune et al. Neuroimage 2002; 17(3): 1256-65) has indicated the presence of an inhibition of metabolite synthesis in the brain of CFS patients, an abnormality that might be one of the keys to unveiling the mechanisms of the chronic fatigue sensation. Again, Tomoda et al (Brain Dev 2000; 22(1): 60-4) using localised MRS and SPECT in the brain of patients with childhood CFS have found indications of a raised choline-creatine ratio in CFS patients.

Finally, Dr Suhadolnik discussed the genetics of CFS, and described a model of the pathogenesis of CFS originally proposed by Keller et al. (Clin Infect Dis 1994; 18 Suppl 1: S154-6) which included the suggestion that there is a genetic predisposition which, coupled with a triggering event, leads on to immune dysregulation and chronic immune-activation, or to secondary viral reactivation. At the University of Washington, the CFS twin registry study has been comparing monozygotic and dizygotic twins discordant for CFS, and evidence is beginning to emerge that CFS may be familial. (e.g., Aaron LA et al. J Rheumatol 2002; 29(11); 2426-3, and Sabath DE et al. J Infect Dis 2002; 185(6): 828-32). At the moment - as indicated by two of the research abstracts at the AACFS conference - novel work is being conducted with microarray analysis to assess the usefulness of gene expression profiling from the blood of people with CFS. It remains to be seen whether this technique will uncover a biomarker for CFS or indicate a genetic predisposition for the illness.

Presentations on Biochemistry

- ***Utility of the Blood for Gene Expression Profiling and Biomarker Discovery in CFS*** Suzanne D. Vernon et al. Division of Viral and Rickettsial Diseases, National Centre for Infectious Diseases, Centres for Disease Control and Prevention, Atlanta, GA Since there is no obvious "lesion" in CFS, investigation is hampered by the lack of a "sample" to test. However, demonstration of the utility of the blood for gene expression profiling would have implications for the pathophysiology of CFS. Dr Vernon remarked that her investigation represented a "proof of concept" study to determine if gene expression profiles of peripheral blood mononuclear cells (PMBCs) could distinguish between subjects with CFS and healthy controls. Total RNA from PBMCs of twenty-five CFS cases and seventeen controls was labelled and hybridized to 1764 genes on filter arrays. Gene intensity values were analyzed by various classification algorithms and nonparametric statistical methods. The classification algorithms grouped the majority of the CFS cases together, and distinguished them from the healthy controls. Seven genes were differentially expressed in both an age-

matched case-control analysis and when comparing all CFS cases to all controls. Several of the differentially expressed genes are associated with immunologic functions (e.g., CMRF35 antigen, IL-8, HD protein) and implicate immune dysfunction in the pathophysiology of CFS. AUTHORS' CONCLUSION: These results successfully demonstrate the utility of the blood for gene expression profiling to distinguish subjects with CFS from healthy controls, and for identifying genes that could serve as CFS biomarkers.
PUBLICATION: Vernon SD et al. Utility of the blood for gene expression profiling and biomarker discovery in Chronic Fatigue Syndrome. Dis Markers 2002; 18(4): 193-9.

Gene Microarray Analysis of Muscle Biopsies from Patients with Chronic Fatigue and Myalgia Wilhelmina M.H. Behan et al. Department of Pathology and Neurology and Centre For Exercise Science and Medicine. Glasgow University, Glasgow, United Kingdom. Dr Behan's presentation described a study comparing muscle from patients with fatigue due to different chronic diseases, using microarray technology to establish whether or not there is a common profile of gene expression. Biopsies were collected from the vastus lateralis of patients with CFS (n=18), chronic obstructive pulmonary disease (COPD) (n=18), acute inflammatory myopathy (n=10) and healthy sedentary individuals matched for age and habitual levels of physical activity (n=10). She stressed that age and gender matching were very important in such studies. Comparison between the groups identified a range of genes that were differentially expressed (more than 3-fold). In CFS, 33 genes were downregulated and 3 upregulated. Various elements of the insulin-like growth factor and calcineurin signal transduction pathways were upregulated (e.g. IGF-BPI 0, NF-AT and MEF2) in the arrays. In addition, 24 transcripts have been found to be present in controls but not in patients. At present, there is no obvious "cluster" or "signature" but work is continuing to confirm these expression profiles using standard molecular biology techniques.
AUTHORS' CONCLUSION: The symptoms of fatigue and myalgia experienced by patients with CFS are similar to that in other common conditions such as COPD and chronic heart failure (CHF92). Functional and histological studies a consistent with profound deconditioning in all these patient groups although it is apparent that additional mechanisms are also involved in pathogenesis. Many of the factors that are differentially expressed in these arrays have been implicated in the regulation of muscle repair. These data may suggest a role for such factors in the pathogenesis of fatigue and myalgia in a range of chronic disease states where fatigue and myalgia are problems.

Increased Plasma Isoprostanes and Other Markers of Oxidative Stress in Chronic Fatigue Syndrome Gwen Kennedy et al. Vascular Diseases Research Unit, University Department of Medicine, Ninewells Hospital & Medical School, Dundee, Scotland. Dr Kennedy explained that recent evidence points to excessive free radical generation in the pathogenesis of CFS. While free radicals may generate tissue oxidative injury, it is now clear that other oxidative by-products, especially peroxidised lipids such as isoprostanes formed by catalysed peroxidation of arachidonic acid, may be even more pivotal in the pathological process. Isoprostanes can exert potent biological activity, are powerful vasoconstrictors of the peripheral vasculature, and they act as mediators of the cellular effects of oxidative injury. Other indicators of lipid peroxidation are oxidised low-density lipoproteins (oxLDL) and low levels of high-density lipoproteins (HDL). Glutathione (GSH), on the other hand, is the major endogenous antioxidant produced by cells and it plays a vital role in determining vulnerability to cellular attack by free radicals. GSH plays a major role in the detoxification of various pollutants and toxins and low levels of GSH are associated with various conditions such as immune dysfunction and cardiovascular diseases. The objective of this study was to investigate lipid peroxidation in CFS by examining isoprostanes, oxLDL and HDL levels in conjunction with a measure of GSH. She examined forty-seven patients who fulfilled the Centres for Disease Control criteria for CFS, and 34 sex and aged matched healthy volunteers were recruited. The following markers of oxidative stress were determined from a blood sample: red blood cell GSH levels were measured on a spectrophotometer; oxLDL levels were measured by ELISA; plasma isoprostanes were measured by gas chromatography-mass spectrometry; and high density lipoproteins (HDL) levels were measured on a Cobas Bio centrifugal analyser. The results showed that CFS patients have significantly increased levels of isoprostanes ($P<0.005$) and oxLDL ($p=0.02$), indicating a direct measure of lipid peroxidation and oxidative stress. CFS patients also had lower levels of the antioxidant GSH and lower levels of HDL ($P<0.001$). AUTHORS' CONCLUSION: These new data provide further evidence of dysfunction of the oxidative pathways in CFS. The finding of high levels of isoprostanes in patients with CFS is particularly important given their sensitivity, reliability and correlation with other measures of lipid peroxidation in vitro. Furthermore, isoprostanes may not only be markers of oxidative injury, but may in fact mediate the effects of free radicals and reactive oxygen species via their ability to act as potent vasoconstrictors. Such findings may have a particular resonance to many of the symptoms of CFS. The work was supported by MERGE (UK Charity 1080201).

Antioxidant Status in CFS. Delia Racciatti et al. Clinic Infectious Diseases and Centre for Atherosclerosis Prevention- "G. D'Annunzio" University, Chieti (Italy). Given the recent interest in oxidative stress in CFS, and the publication of a novel theory by which elevated peroxynitrite may represent the cause of CFS (Pall ML. Med Hypoth 2000, 54: 115-125), Dr Racciatti presented the results of a study to determine the oxidant-antioxidant status in CFS patients and its impact on CFS pathogenesis. In total, 21 patients with CFS, including 7 with a concurrent Fibromyalgia, and 20 healthy subjects were selected at the National Reference Centre for CFS Study of Chieti University. All subjects underwent a diagnostic protocol including the evaluation of oxidant/antioxidant status measuring tbiobarbituric acid reactive substances (TBA-RS), the Lag-Phase and the susceptibility of lipoproteins to oxidative attack in vitro, and vitamin E plasma content. CFS patients showed higher levels of TBA-Rs and lower levels of Lag-Phase than controls (0.431±0.20 vs 0.229±0.06 and 96.09±25.78 vs 115.35±12.06, respectively) in a statistically significant way ($p < 0.0001$). Also vitamin E plasma content was reduced in CFS patients when compared with healthy subjects (33.06±16.31 vs 44±5.46; $p<0.006$). AUTHORS' CONCLUSION: CFS patients seem to be characterized by an imbalance of oxidant/antioxidant status with a consequent oxidative stress due to an oxidant attack by free radical production in association with an insufficient antioxidant defence. This hypothesis is supported by the authors' previous study in which such oxidative damage was described in muscle biopsies of CFS patients. So, the role of oxidative stress in CFS represents an important area for current and future studies in order to lead to a better comprehension of pathophysiological mechanisms involved in CFS onset, and to identify potential therapeutic approaches (e.g., antioxidant agents).

LECTURE: John Hay, PhD. Current Status of Infectious and Immunological Hypotheses Causing Unexplained Illness

Prof Hay presented a brief overview of putative infectious and immunological influences on the development of CFS. He noted that many people with CFS report an infectious onset to their illness, and that infectious illnesses tend to involve symptoms similar to those defining CFS. He reported that, over the years, some 30 infectious agents have been implicated in the causation or maintenance of CFS. Examples include HHV6 and 7, for which there is currently little good evidence of involvement in CFS; bornavirus, which has been found in relatively few people with CFS; *Borrelia* spp., involved in Lyme disease but most probably not in most cases of CFS; mycoplasma, for which approx one third of people with CFS have been found to be positive (Vojdani et al. FEMS Immunol Med Microbiol 1998; 22(4): 355-65); and parvovirus B19 infection which does not appear to result in CFS in most patients (Kerr et al. J Rheumatol. 2002; 29(3): 595-602). In short, Prof Hay reported that, overall, we can identify no consistent single infectious agent or obvious pattern of infection leading to the development of CFS.

As regards cellular immunity, it is known that cytokine administration can induce CFS-like symptoms, and that cytokines, such as TNFα and IFNγ, can be disrupted during infection. Levels of some cytokines have been studied in CFS, though at the moment little can be definitively concluded: one investigation on IL-1β and IL-6 (Cannon et al. J Clin Immunol 1999; 19(6): 414-21) suggested that cytokine dysregulation is not a singular or dominant factor in the pathogenesis of CFS, while another on TNFα (Moss et al. J Clin Immunol 1999; 19(5): 314-6) found a significant increase in serum levels in people with CFS. Again, in other work (e.g., Repka-Ramirez et al. Allergy Asthma Proc 2002; 23(3): 185-90) IgE levels have not been shown to be significantly altered in people with CFS. The link between autoimmunity and CFS is superficially promising, yet whereas von Mikecz et al. (Arthritis Rheum 1997; 40(2): 295-305) found a high rate of autoantibodies to a conserved intracellular protein, there has recently been a large negative trial (Skowera et al. Clin Exp Immunol 2002; 129(2): 354-8). Natural killer cells have been widely investigated in CFS, and the consensus is that the activity of these cells is, on the whole, decreased in people with CFS, though the quality of evidence is variable. Interestingly, a recent study by Sabath et al. (J Infect Dis 2002; 185(6): 828-32) found no difference in natural killer activity between twins with CFS and their healthy controls.

Prof Hay explained that at present there is no consensus on a central model of immune dysfunction in people with CFS. The way forward may involve sub-grouping patients by factors, such as mode of onset of illness, since there may be many physiological routes to the final diagnosis of CFS.

Presentations on Infection/Immunology

- ***Molecular Defects Associated with CFS***

Kevin Maher et al. Department of Medicine, University of Miami School of Medicine and the Veterans Administration Hospital, Miami, FL. Dr Maher described his work to determine the molecular mechanisms underlying the decreased natural killer cell cytotoxicity observed in his laboratory. Thirty-six case defined CFS subjects and 35 healthy controls were evaluated for the expression of lymphocyte cell surface molecules and intracellular cytokines by standard flow cytometry, and for the intracellular expression of cytolytic proteins by quantitative flow cytometry. Subjects with CFS demonstrated significantly elevated expression of the activation molecule CD26 on T-helper

cells and significantly reduced NK cytotoxicity relative to controls. CFS subjects also demonstrated decreased % CD 11a+ NK cells and increased % CD62L+ T cells. Perforin expression in NK cells was significantly reduced relative to controls. Also, perforin, granzyme A and granzyme B were significantly reduced in cytotoxic T cells of CFS subjects. These findings are especially interesting as perforin, granzyme A and granzyme B are used by T-cells for cytotoxic activities. AUTHORS' CONCLUSION: These results demonstrate an inverse correlation between lymphocyte activation and the expression of cell-associated proteins and cytokines necessary for the cytolytic process. These findings substantiate claims of an NK-associated defect in CFS and suggest a molecular basis for the reduced cytotoxicity. In addition, the data suggest that the cytotoxic defect may not be NK specific but may encompass the cytotoxic T cell subset as well.

• ***White Blood Cells from Patients with Chronic Fatigue Syndrome Exhibit Distinct Gene Expression Profiles*** Patrick M. Gaffney et al. Department of Medicine, University of Minnesota, Minneapolis, MN. Dr Gaffney described a "proof of principle" study designed to test the utility of peripheral blood cell gene expression analysis in people with CFS. To date, samples have been collected from 22 people fulfilling 1994 criteria for CFS and 16 matched healthy control individuals. Blood was collected into Paxgene tubes for the immediate isolation and stabilization of total RNA and processed according to methods specified by Affymetrix, Inc. for gene expression studies. Those transcripts demonstrating a difference in gene expression exceeding $p<0.001$ were selected, yielding 54 genes. In this ongoing study, there were a number of genes that showed very discordant expression between CFS and control WBCs. Some of the more interesting genes include B-cell CLL/lymphoma 6 (bcl-6), an oncogene for B lymphocytes; homeodomain-interacting protein kinase 2, recently shown to selectively phosphorylate p53 at serine 46 thus stimulating cellular apoptosis in response to UV radiation; and carcinoembryonic antigen-related cell adhesion molecule 3 (CEACAM3), a member of the CD66 complex on human neutrophils implicated as a cellular receptor promoting phagocytosis of microorganisms. A number of genes without any specific defined function (e.g., KIAA0453) were also differentially expressed. AUTHORS' CONCLUSION: These results demonstrate differential regulation of 54 genes ($p<0.0001$) between patients with CFS and normal healthy control subjects. Several new potential candidate genes have been identified in this analysis as well as additional evidence implicating the IL-1 pathway in the etiology of CFS. Given the recent FDA approval and clinical introduction of IL-1 receptor antagonists for treatment of rheumatoid arthritis, one can appreciate how a result like this, if it can be confirmed in a much larger sample, could be quickly moved to the clinical realm. Studies aimed at increasing the sample size of CFS patients and control subjects, applying additional data analysis methods and confirming the gene expression data using complementary methods are underway.

• ***Chronic Fatigue Syndrome is Distinct From Depressed Healthy Controls: Biochemical and Clinical Differences*** Robert J. Suhadolnik et al. Temple University School of Medicine, Philadelphia, PA. Dr Suhadolnik described how the study was designed to investigate the relevance of dysregulation of the 2-5A/RNase L pathway to the clinical presentation of CFS. Individuals with a confirmed diagnosis of CFS were selected for a double-blinded study and compared with healthy and depressed controls. There were 67 CFS subjects, 60 healthy age and sex-matched controls, and 52 depression controls. The three groups showed a high level of separation using all chemical and clinical parameters. CFS subjects, depressed subjects and controls were predicted with a 79%, 66% and 77% accuracy respectively. One CFS patient and one depressed patient were misassigned by this technique. There was also an increase in upregulated 37-kDa RNase L in CFS study subjects compared with the depressed controls. The IFNα, 2-50AS, RNase L and serum chemistry variables were placed into a discriminant function analysis that gave a strong model. Elevated 37-kDa RNase L was the principle discriminant variable ($p < 0.016$), followed by total RNase L activity ($p<0.024$), serum creatinine concentration ($p<0.03$) and serum alkaline phosphatase activity ($p<0.04$). Multivariate analysis also showed that - using these biochemical parameters - the three study groups were also very distinct, with 79% correlation of the data. The mean for the 37-kDa RNase L for the CFS group was significantly elevated compared to depressed controls and healthy controls. AUTHORS' CONCLUSION: The close association of the upregulated 2-5A/RNase L innate immune defense pathway and the clinical presentation of CFS is consistent with the authors' earlier clinical studies and studies from other laboratories. The results demonstrate the utility of measurement of the 37-kDa RNase L to distinguish CFS patients from healthy controls and depressed controls. Biochemical markers can be used together with clinical parameters identify CFS patients and to identify homogeneous subsets within the population. This CFS identification and subset approach could lead to further studies of the unique attributes of each subset. It could also be useful in studies to determine the effectiveness of treatment methodologies targeted for each subset This research was supported by NIH research grant R01 AI38378

LECTURE: Benjamin H. Natelson, MD. Treatment Trials in Medically Unexplained 1Ilness

Dr Natelson illustrated some of the difficulties in running clinical trials with reference to a large multicentre RCT of modafinil (Provigil®) trial for CFS symptoms. Modafinil, which is said to enhance wakefulness and vigilance, is used to treat fatigue and drowsiness, and has been found useful for MS and Fibromyalgia patients. However, after the 4-week, 6-centre trial, with a modafinil dose of 200 mg, there was little evidence of efficacy for people with CFS. The drop-out rate was quite high (20%), with patients reporting nausea and headaches as the main reasons. Interestingly, two of the centres had better results than others, and Dr Natelson speculated that certain local factors may have contributed towards a placebo effect.

Since other clinicians have reported modafinil useful for cognitive symptoms, Dr Natelson thought that several flaws in the study could have contributed to a false negative result. The outcome measures chosen may not have been ideal for a CFS patient group, the timescale of treatment and assessment may have been sub-optimal, and the inclusion of 6 centres - rather than one - may have complicated the trial unnecessarily. Again, choice of patients may have been problematic: it might (in this case) have been preferable to include only patients reporting a sudden onset of symptoms consistent with an infectious illness, and to exclude those exhibiting a high rate of co-morbid illness.

Presentations on Treatments

Treatment of staphylococcus toxoid in FM/CFS - a randomized controlled trial Olaf Zachrisson et al. Institute of Clinical Neuroscience, Goteborg University, Goteborg, Sweden. Dr Zachrisson described a clinical trial designed to assess the efficacy of the staphylococcus toxoid vaccine, Staphypan Berna (SB) over 6 months in FM/CFS patients. One hundred consecutively referred patients fulfilling the ACR criteria for FM and the 1994 CDC criteria for CFS (51 with CFS) were randomized to receive active drug or placebo. Treatment included weekly injections containing 0.1, 0.2, 0.3, 0.4, 0.6. 0.8, 0.9 and 10 ml SB or coloured sterile water, followed by 4-weekly booster doses until endpoint. The treatment was well-tolerated. Intention-to-treat analysis showed 32/49 (65%) responders in the SB group compared to 9/49 (18%) in the placebo group (P 0.001). Sixteen patients (33%) in the SB group reduced their CPRS scores by at least 50% compared to 5 patients (10%) in the placebo group (P<0.01). An increase in CPRS symptoms at withdrawal was noted in the SB group. AUTHORS' CONCLUSION: Treatment with staphylococcus toxoid injections over 6 months led to significant improvement in patients with FM and CFS. Maintenance treatment is, however, required to prevent relapse.

Effectiveness of Aerobic Exercise and Cognitive Behavioural Therapy in 1092 Veterans with Chronic Multisymptom Illnesses: Results from CSP #470 Daniel J Clauw et al. University of Michigan, Ann Arbor, MI. Dr Clauw outlined a study designed to test the effectiveness of cognitive behavioural therapy (CBT) and aerobic exercise for symptoms and functional status of individuals who have the constellation of persistent pain, fatigue and cognitive symptoms that has been termed Gulf War veterans illnesses (GWVI). To be eligible, veterans had to endorse >2 of the following symptoms: 1) fatigue limiting usual activity, 2) pain in >2 body regions, and 3) neurocognitive symptoms. In total, 1092 veterans with GWVI were enrolled, and randomly assigned to one of four treatment arms: CBT plus exercise, exercise alone, CBT alone, and usual care. Treatments were given for three months using standard protocols and participants were evaluated at baseline, 3, 6 and 12 months. The primary endpoint was the proportion of participants who improved more than seven units on the physical component summary scale of the Veterans Short Form 36-item (SF-36) Health Survey at 12 months after randomization. The results revealed no significant differences in the proportion of veterans who reported an improvement in physical function at one year among the treatment groups (11.5% for usual care 11.7% for exercise, 18.4% for CBT and 18.5% for CBT + exercise). However, modest but statistically significant improvements in fatigue, cognitive symptoms, distress, and mental health functioning were observed with exercise alone, and with exercise plus CBT compared to usual care. CBT alone had a statistically significant effect on cognitive symptoms and in mental health functioning. With the exception of the affective dimension of pain, which was improved with CBT alone and CBT + exercise, the three other pain measures were not improved with treatment. AUTHORS' CONCLUSION: Neither aerobic exercise nor CBT had a significant impact on self-reported physical function for veterans with GWVI, but both treatments, especially exercise, resulted in improvement in fatigue, cognitive symptoms, distress and mental health functioning.

Low intensity, interval training in women with Chronic Fatigue Syndrome Claudia Lennartsson et al. Dept of Physical Therapy, Huddinge University Hospital Stockholm, Sweden. Dr Lennartsson explained that the objective of this study was to evaluate the effects of low-intensity interval training in women with CFS. Twenty-four women fulfilling the CDC case criteria for CFS participated in the study. The patients were divided in two groups; a training group and a control group, and they trained for 10 weeks according a standardized walking programme. Functional exercise capacity was measured by the shuttle walking test (SWT) and the six-minute walk test (6MW). The subjects completed

various standard questionnaires, including the SF36, in order to assess functional status, quality of life, mental and physical fatigue, health status and coping capacity. The assessments were performed at baseline and after 10 weeks. Significant differences were found after the training period in SWT and in the physical function variable assessed by the SF-36. However, no inter-group differences between the training group and the control group could be found either in walking tests or in quality of life. All the CFS patients had low scores in physical functioning and health related quality of life compared with healthy women. The fatigue rates in the control group increased during the study period and significant inter-group differences were found. AUTHORS' CONCLUSION: Light intensity interval training for CFS patients can be beneficial and slowly produce improvements in their exercise capacity and physical functioning without increased fatigue. Compliance was good. Exercising did not exacerbate the CFS symptoms which allowed the patients to do their program without fearing relapses. Studies with extended training period and long-term evaluations with larger populations are recommended.

LECTURE: Trudie Chalder, PhD. Psychosocial Factors in Unexplained Illness.

Dr Chalder described some of the problems surrounding diagnostic labelling in the "medically unexplained illnesses". While a variety of terms - ranging from somatisation to conversion disorder - are used, it may be more instructive to sub-divide this diagnostic construct into those which are associated with functional physiological changes, albeit of unknown etiology; those which can more properly be termed medically unexplained; and those which inhabit an intermediate sub-group. She stressed the importance of the investigation of cognitive and behavioural factors as well as physiological processes since "stressors", such as life events, and psychological fitness can be important determinants of fatigue in an individual. Describing the use of questionnaires, she noted a past investigation which showed that the level of fatigue could be predicted by the perceived lack of practical support, and she stressed that cognitive behavioural therapy could address factors with a strong emotional or cognitive component.

Presentations on Biosocial Aspects

Subgroups of Fibromyalgia patients based on pressure pain thresholds and psychological factors Thorsten Giesecke et al. University of Michigan, Ann Arbor, MI. This investigation was carried out to determine if subsets of FM patients could be identified by combining psychological and cognitive variables with measures of tenderness, independent of psychological status. Mood, [CES-D (depression), STPI (trait anxiety)], cognitive function [the CSQ catastrophic control subscales] and tenderness - assessed by pressure pain threshold [dolorimetry and random pressure supra-thresholds (RPS) values] - were evaluated in 97 individuals who met ACR criteria for FM. Patient subgroups were formed using agglomerative hierarchical cluster analysis, and Ward's method was used to form clusters at each stage. Three clusters best fit these data and MANOVA confirmed that each variable was differentiated by the cluster solution. One subgroup (n=31) was characterised by clinically significant elevated values for anxiety and depression, the highest values on catastrophizing, the lowest values of personal control over pain, and considerable tenderness. A second subgroup (n=50) was characterized by normal mood ratings, low levels of catastrophizing, moderate levels of personal control pain and significantly higher thresholds for pain. The third group (n=16) also had normal mood ratings, very low levels of catastrophizing, and the highest level of perceived control over pain but were extremely tender. AUTHORS' CONCLUSIONS: These data support the clinical impression of distinct subgroups of patients with FM. There appears to be a group of FM patients that is extremely tender with no identifiable psychological/cognitive contribution, an intermediate group that is moderately tender and has normal mood, and a group where mood disorders and cognitive factors may be contributing considerably to their tenderness.

Outcomes of a consumer-driven rehabilitation program for individuals with CFS: a randomized clinical trial

Renee R. Taylor et al. Dept of Occupational Therapy, University of Illinois, Chicago, IL. Dr Taylor described a study designed to evaluate the effects of an empowerment-oriented rehabilitation program on quality of life, resource acquisition, and other outcomes for individuals with CFS related to symptoms and disability. Forty-seven adults with CFS participated in a 12-month rehabilitation program designed to improve quality of life and other outcomes. The program, which was conducted within a centre for independent living, involved three components: assessment, illness management groups, and one-on-one case coordination/peer counselling. Twenty-three of the 47 participants were randomly assigned to the immediate treatment group and 24 were randomly assigned to the delayed treatment control group. Outcomes were measured for all participants at three time points: baseline, after the illness management groups, and after the one-on-one phase. Individuals in the immediate treatment group exhibited significantly higher overall quality of life and significantly higher quality of life with respect to family functioning following the program as compared with controls that had not yet received the program. In addition, individuals in the immediate treatment group demonstrated significant

total resource gain, gain with respect to general personal resources, gain in energy resources, gain in material resources, gain in personal mastery resources, gain in self esteem, and gain in work resources. Individuals in the immediate treatment group also reported significantly lower symptom severity as compared with the delayed treatment control group. There were no significant differences between groups in functional disability scores. AUTHORS'CONCLUSION: The findings suggest that rehabilitation programs that focus on the principles of empowerment and involve consumer voices in both group and one-on-one forms of therapy may be effective in improving quality of life and resource acquisition, and in reducing symptom severity for individuals with Chronic Fatigue Syndrome.

Mediators of outcomes in veterans with chronic multisymptom illnesses David A. Williams et al. and the CSP #470 study group. University of Michigan, Ann Arbor, MI. Dr Williams described how the results of the VA Cooperative Trial (CSP # 470) demonstrated that while each therapy (exercise or CBT) was successful in improving a subset of the sample, no one therapy was clearly superior. Given that the impact of these interventions was less than expected, this presentation represented a secondary analysis of these data with the aim of identifying baseline factors that influence outcomes for these two treatment modalities. In total, 1092 Gulf War Veterans with CMI were enrolled and study outcomes consisted of functional status, mental health, current pain, general fatigue, and memory problems. The results showed that regardless of treatment, physical functioning, mental health functioning, pain, fatigue, and cognitive problems were worse in veterans with a disability, or a mood disorder. Physical functioning, pain and fatigue were also significantly worse in veterans with higher tender point counts. The effect of exercise in improving physical functioning was significantly greater for males, while the effect of CBT on current pain was significantly greater for females. The patients in the exercise group who displayed the greatest tenderness demonstrated significantly greater improvement for physical functioning and cognitive problems compared to those who were less tender. The effect for CBT was similar, with the more tender veterans showing greater benefit from CBT in physical functioning, fatigue, and pain. AUTHORS'CONCLUSION: Sex, mood disorders, personality disorders, disability issues, and dolorimeter threshold were all significantly associated with negative changes in outcomes over time, irrespective of the treatment, whereas tender point count was predictive of positive outcomes. While some of the negative predictors may not be modifiable, those that are should be targeted for treatment in combination with or before CBT or exercise in order to maximize therapeutic gains in the outcomes under study. This study also suggests that exercise and CBT may produce better outcomes if potential participants are screened for participation on the relevant variables studied.

Posttraumatic stress contributes to cardiovascular dysregulation in gulf war veterans with CFS Arnold Peckerman et al. Centre for the Study of War-Related Illnesses, VA Medical Centre, East Orange, NJ. As previous studies have found that Gulf veterans with CFS have abnormal cardiovascular responses to mental stressors and a lower tolerance of orthostatic stress, the objective of the present study was to determine whether those abnormalities in cardiovascular regulation are made worse by comorbid post-traumatic stress disorder (PTSD). The study participants were 39 Gulf veterans with CFS or idiopathic chronic fatigue (ICF), 16 with CFS/ICF and comorbid PTSD, and 47 healthy controls. The veterans were tested on responses to orthostatic (5 min of active standing), sensory (2-min forehead cold pressor test), and mental (speech and mental arithmetic) stressors. The results indicated that veterans with CFS/ICF and comorbid PTSD had more severe symptoms than veterans with CFS/ICF without PTSD. Analyses of physiological data revealed that veterans with CFS/ICF and PTSD had reduced blood pressure responses to mental tasks, but not to the cold pressor stimulus, and had more precipitous instantaneous declines and slower recoveries in blood pressure after standing up than veterans without PTSD. Blood pressure hyporeactivity to mental stress and impaired responses to standing up were both attributable to impaired control of peripheral vascular resistance. Symptoms of post-traumatic stress were significant predictors of hypotensive orthostatic responses, but not of hyporeactivity to mental stressors, and only in veterans with a significant history of exposure to wartime stress. AUTHORS' CONCLUSION: Posttraumatic stress contributes to dysregulation of cardiovascular responses to mental and orthostatic stress in Gulf veterans with CFS/ICF. The authors' finding of more physical symptoms in Gulf veterans with PTSD is in line with other studies showing that Gulf veterans who served under particularly stressful conditions have had more chronic health problems than their peers who had less difficult assignments. The identified alterations in stress response regulation therefore may provide a physiological basis for increased somatic complaints in Gulf veterans with symptoms of posttraumatic stress.

LECTURE: Daniel L. Peterson, MD. Role of Brain in the Pathogenesis of Medically Unexplained Symptoms

Dr Peterson considered the structural abnormalities which have been identified, i.e., unidentified brain objects (UBOs) that show up on T2-weighted images. While these reports are interesting, UBOs are not specific for CFS, it is difficult to confirm their presence,

and there has been a paucity of brain biopsies at autopsy of people with CFS.

As regards functional abnormalities, Dr Peterson listed alterations to the HPA axis; cognitive impairment; non-restorative sleep; regional hypoperfusion (as determined by SPECT scanning); hypometabolism (at PET scanning); autonomic dysfunction (especially neurally-mediated hypotension); and "perturbation" of brain hormones. In addition, primary or reactivated CNS infections, postulated from symptom profiles, may have an important role in functional abnormalities. Indeed, current outbreaks - such as that occurring from August to September 2002 in USA, associated with fever, headache, nausea and myalgia, and later confirmed as West Nile virus, offer a unique opportunity for prospective study of the development of CFS.

HHV-6, which was identified in some of the patients from the Lake Tahoe outbreak, can become reactivated in some individuals, leading to an encephalitis. The presence of HHV-6 has been associated with CFS (Ablashi DV et al. J Clin Virol 2000; 16(3): 179-91). Dr Pererson described his own work with HHV-6 in a cohort of 135 people with symptoms of encephalitis and abnormal MRI scans. In 27 of the 29 subjects in whom viruses were identified in the CSF obtained from spinal tap (blood tests for HHV-6 being unreliable), HHV-6 was present. These subjects did not respond to antiviral treatment, though 8 of them did show improved SF36 and Karnovsky index scores following IV foscarnet. In an attempt to identify people with CFS who might benefit from identification and treatment of HHV-6 infection, Dr Peterson presented a clinical algorithm which included the presence of prominent CNS symptoms, abnormal MRI/SPECT results and spinal tapping to detect HHV-6.

Presentations on the CNS

Spinal fluid abnormalities in some patients with CFS. Benjamin H. Natelson and Nadine Aktan, CFS/FM Centre and Department of Neurosciences, UMDNJ-New Jersey Medical School, Newark NJ 07103. Dr Natelson described earlier research which has begun to accumulate evidence in favor of the hypothesis that some CFS patients may have a covert encephalopathy. First, CFS patients without comorbid Axis I psychiatric disorders had more neuropsychological dysfunction than CFS patients with this comorbidity or controls (DeLuca et al. J Neurol Neurosurg Psychiatry 1997; 62(2): 151-5). Next, CFS patients without comorbid Axis I disorders had the most brain MRI abnormalities (Lange et al., J Neurol Sci 1999; 171(1): 3-7). Finally, preliminary evidence exists indicating that ventricular volumes are larger in CFS than in controls (Lange et al., Appl. Neuropsych 2001; 8: 23). These data lead to the speculation that abnormalities would be found in spinal fluid in CFS patients, especially those without comorbid Axis I, and that patients with abnormalities would have worse cognitive function than those with normal cerebrospinal fluid (CSF). To investigate the matter further, spinal taps were performed to collect lumbar CSF from 39 CFS patients and 5 healthy controls, though as the study is ongoing the final number of study subjects will be greater tah these numbers. The fluid was analyzed for white blood cell count and protein. It was found that healthy controls had 3 or fewer WBCs and proteins not exceeding 30. Eleven CFS patients had proteins in the abnormal range, and 4 had elevated WBCs alone. Thus, 39% of CFS patients had spinal fluid constituents in the abnormal range. There was no difference in current Axis I or lifetime Axis I psychopathology in those with either spinal fluid abnormality compared to those without abnormality. Contrary to the hypotheses, differences in cognitive function as assessed by neuropsychological testing among the groups have not as yet been found. AUTHORS' CONCLUSION: Finding that the spinal fluid of 39% of CFS patients is in the abnormal range for either protein or cells supports the hypothesis that some CFS patients have an underlying pathologic brain process responsible for their symptoms. However, with the current sample size, the authors were unable to correlate patients with CSF abnormalities with psychiatric or cognitive status and are continuing to accrue subjects in this study. This work was supported by NIH Centre grant #AI-32247.

FMRI analysis of constant pressure in patients with Fibromyalgia and Chronic Fatigue Syndrome. Richard Gracely et al. University of Michigan, Ann Arbor, MI. Dr Gracely described how, in this study, the effect of constant pressure stimulation was compared in patients with Fibromyalgia and Chronic Fatigue Syndrome and in healthy controls. Pre-determined stimulus pressures were applied to the thumb nail bed by 1-cm diameter probe during alternating 25s blocks of pressure and pressure release. FMRI scans were performed at 5s intervals. Analysis of the BOLD signal was performed using Medx. The results indicated that in control subjects (n=11) a mean of 4.50 kg pressure evoked pain sensations rated as 14.4 for intensity and 12.5 for unpleasantness using 0-20 numerical/verbal box scales. In patients (n=16), a significantly decreased mean stimulus pressure of 2.81 kg (p=0.011) evoked sensations rated as 16.7 (p=0.21) for intensity and 14.8 (p=0.20) for unpleasantness. In patients, pressures sufficient to evoke slightly intense pain resulted in significant increases of BOLD signal in ipsilateral putamen and cerebellum, contralateral caudate nucleus, inferior frontal gyrus BA45, inferior parietal lobule BA40, and in bilateral medial frontal gyrus BA46. In contrast, the activations in healthy controls were restricted to the ipsilateral cerebellum and contralateral inferior parietal lobule BA40. Statistical comparison between groups revealed significant differences in

BOLD signal in the contralateral medial frontal gyrus BA 10/46, cerebellum and inferior parietal lobule BA40. AUTHORS' CONCLUSION: Despite significantly lower stimulus pressures, the patients showed a trend for higher subjective ratings and significantly increased cerebral responses to the constant stimulus. These results suggest that these patients show a hyperalgesic response to the changed stimulus condition that is reflected both in subjective ratings and evoked cerebral activity. This simple method may provide a useful tool for the analysis of the underlying mechanisms in Chronic Fatigue Syndrome and related disorders.

Event related potentials abnormality in Japanese childhood CFS (CCFS) Akemi Tomoda et al. Department of Child Development, Kumamoto University School of Medicine, Kumamoto, Japan. Dr Tomoda reported that 5% of high school students and 20% of junior high school students exhibited CFS symptoms, especially cognitive dysfunction and fatigue. He advised that he had previously reported the decreased regional cerebral blood flow, expressed as the corticocerebellar ratio (CCR), in Japanese childhood Chronic Fatigue Syndrome (CCFS) using xenon-computed tomography (Tomoda et al. Brain Dev 2000; 22(1): 60-4). In the test, however, the decrease of high order functions for the information processing in their brains could not be objectively shown. Therefore, to examine these functions in the brain in normal children and CCFS, his group analyzed event related potentials (ERPs) using a visual oddball paradigm. In total, 264 healthy children (control) and 319 CCFS, aged from 6 to 18, participated in this experiment. To investigate the autonomic nervous function studies, the component analysis of cardiographic R-R interval in controls and each type of the CCFS patients were examined. CCFS were divided into three types (Type I, II and III). In Type I (n=53), the latency of ERPs to target stimuli was significantly more prolonged ($P<0.001$) than that in controls. In Type II (n=63), the latency of ERPs to target stimuli was significantly ($P<0.001$) shorter, and the amplitude of ERPs to non-target stimuli was significantly ($P<0.001$) larger, compared with each result in controls. In Type III (n=203), latencies and amplitudes of ERPs to target and non-target stimuli were not significantly different, compared with those of ERPs in controls. The cardiographic R-R interval study revealed significant suppression of the peak of HFC (parasympathetic component) in the patients with CCFS. AUTHORS' CONCLUSION: Type I may be a delayed type which has a possibility of child dementia. Type II may be a hypersensitive type. Type III may be a mild type. This type did not exhibit the abnormality of high order functions in the brain, but signified the abnormality of functions in the autonomic nervous system.

LECTURE: Yoshiharu Yamamoto, Ph.D. Technological Advances in Researching Medically Unexplained Illness

Dr Yamamoto described three recent technological advances: the use of stochastic resonance for assessment of baroreflex and neurological responses (Hidaka, et al, Phys Rev Lett 2000; 85: 3740); improvements in analysis of time series data from studies of locomotor activity in people with CFS; and the development of a new watch-type computer - the ECOLOG. The first development can be useful for the assessment of autonomic dysfunction (and, indeed, has been reported to be useful for the modest improvement of symptoms through the supply of stochastic resonance), the second for the interpretation of continuous longitudinal activity data, and the last for behavioural studies on people with CFS.

The ECOLOG is a watch-type computer for ecological momentary assessment of patients' moods, physical symptoms and cognitive functions. In addition, it has a built-in actigraph for locomotor activity data, it emulates the windows directory tree, and allows continuous operation for >30 days. It has shown promising results in early trials (e.g., Ohashi et al. Physiol Behav 2002; 77(1): 39-44).

Presentations on Technology

Development of a new watch-type computer for ecological momentary assessment and application to CFS patients. Kazuhiro Yoshiuchi et al. Department of Neurosciences, University of Medicine and Dentistry of Jersey - New Jersey Medical School. Dr Yoshiuchi described the development of the ECOLOG, a wearable watch-type computer device. The ECOLOG can collect and log data on subjective symptoms, cognitive function, and activity. The device is currently used to track symptoms before and after CFS patients perform exercise tests. The watch type computer is programmed for an electrical diary, a continuous performance task (CPT), and for measuring activity. The diary asks questions concerning physical symptoms such as fatigue, sore throat, and tender glands, and mood states such as depression and nervousness. The wrist mounted computer operates approximately every four hours. Following diary entry, the CPT - consisting of a one back memory task for three minutes - is administered. Activity is measured continuously with an accelerometer. Data is currently being collected from patients with CFS and healthy controls who wear the device one week before a maximal exercise test, and for two weeks after the test. Preliminary results indicate that people with CFS, in contrast with healthy subjects, have short bursts of intense activity followed by rest. AUTHORS' CONCLUSION: A new watch-type computer device for ecological momentary assessment has been developed, and it appears useful in evaluating

the daily pattern of symptoms, cognitive function, and activity in CFS patients.

Ambulatory activity monitoring: evidence for reduced peak activity and associations with symptomatology Angela Lyden et al. Division of Rheumatology, University of Michigan. Dr Lyden described the use of objective automated activity monitoring to document altered physical activity levels in patients during daytime activities and sleep, and to assess associations between objective measures of physical activity with ambulatory symptoms of pain, fatigue and distress. Study participants were 25 patients and 18 controls not engaging in high-exercise activities. Actigraphs were worn for 5 consecutive days and activity levels were sampled over 5 min epochs. Participants also rated symptoms ("pain", "tired", "stressed") on 10-point scales 5 times/day based on actigraph-driven alerts. Average and peak levels were calculated for physical activity during daytime hours and during sleep. Patients had significantly lower peak activity levels (8771 +/- 3717 units) compared to controls (13459 +/- 7515 units; p=023). The average daytime or nocturnal activity levels did not differ between the two groups. Variability of peak activity level over the 5 day period was significantly larger in patients than in controls. Both peak and average symptoms were significantly higher in patients than in controls. Among the patients, average daily or nocturnal activity levels were not significantly related to pain and fatigue. Average daily activity was positively related to peak distress, and nocturnal activity was predictive of subsequent morning distress upon awakening and one hour post awakening. AUTHORS' CONCUSION: Using objective measures of physical activity, this study demonstrates reduced peak activity levels in a group of patients with CFS and/or FM. Associations between objective ambulatory activity levels and ambulatory pain and fatigue were generally weak in both patients and controls. Future studies will examine circadian patterns time trajectories of activity levels and subsequent symptomatolgy.

LECTURE: Phil Gold, MD. HPA Function Differs in Depressed People from Those with CFS

Dr Gold addressed the differences in neuroendocrine function between people with CFS and those with depression. Physiologically, people with depression show elevation of the 24-hour norepinephrine levels in cerebro-spinal fluid and the 24-hour cortisol levels in plasma; a decrease in reproductive function; raised heart rate and blood pressure; and some degree of immunosuppression. By contrast, people with CFS exhibit decreases in adrenocorticotropic hormone (ACTH) - which stimulates the adrenal cortex and is secreted in response to many types of stress - and therefore decreases in plasma cortisol levels. In addition, blood pressure is often reduced in people with CFS.

Clinically, people with severe depression show anxiety, lethargy and anhedonia. However, there are cases of "atypical depression" in whom profound fatigue, including increased drowsiness, is manifest (Gold PW et al. Mol Psychiatry 2002; 7(3): 254-75, and Am J Psychiatry 2002; 159(11): 1826): in these people ACTH and cortisol levels can be reduced (as in CFS), but they nevertheless exhibit social withdrawal and anhedonistic behaviour, unlike many people with CFS. Dr Gold postulated that there was more inhibition of the hypothalamic-pituitary-adrenal (HPA) axis in people with CFS than in those with atypical depression. He also noted that there is some evidence that exercise (a stressor in CFS) can induce reductions in ACTH and plasma cortisol in people with CFS (Gaab J et al. Psychosom Med 2002; 64(6): 951-62), indicating a dysfunction of their stress responses.

Presentations on Physiology

Peripheral factors affecting blood flow and venous return in adolescents with CFS Julian M. Stewart. Departments of Pediatrics and Physiology, New York Medical College, Valhalla, NY 10595. Dr Stewart reminded the audience that CFS is associated with postural tachycardia (POTS) in adolescents, and that prior work has indicated that blood flow and venous return is impaired in adolescents with CFS/POTS. Accordingly, he sought to assess the adequacy of two local mechanisms affecting blood flow in patients with CFS/POTS: metabolic mediated maximal vasodilation assessed by reactive hyperaemia, and the skeletal muscle pump. Fourteen patients fulfilling the Fukuda criteria for CFS and 9 age- and gender-matched healthy control subjects were included, age = 16±1.5 years. The calf skeletal muscle pump was assessed by the method of Nicolaides using calf strain gauge plethysmography and leg lift during supine rest to determine minimum limb volume and then quiet standing to fill calf veins. Emptying of the calf was assessed by single and then 10 consecutive "tiptoe" movements to define the expelled volume of the limb. After 30 minutes of supine rest, reactive hyperaemia was effected by inflating a thigh occlusion cuff to 20 mmHg above the measured systolic arterial blood pressure in the leg. The cuff remained inflated at pressure for 4 minutes, was then rapidly deflated, and multiple rapid sequential inflations were performed at 50 mmHg to obtain measurements of calf blood flow by standard means via fitting the slope of volume change. The results showed that there was no difference between CFS and control subjects in the fractional expelled blood from the calf but a markedly decrease in absolute expelled volume in individual patients consistent with a change in venous capacitance ("low-flow POTS"). No difference was noted in maximum hyperaemic flow while the decrease from maximum flow exceeded control. AUTHORS' CONCLUSION: Calf venous capacity is reduced

without obvious deficit in the skeletal muscle pump, maximum hyperaemic flow is preserved. Hyperaemic flow is a measure of the maximum ability for arteriolar vasodilation and suggests that arterial remodeling does not occur in patients with CFS/POTS.

Prolonged action of acetylcholine induced vasodilatation in blood vessels of patients with CFS Vance A. Spence et al. Vascular Diseases Research Unit, University Department of Medicine, Ninewells Hospital & Medical School, Dundee DD1 9SY. Dr Spence explained that many of the symptoms of CFS involve various aspects of muscarinic and nicotinic cholinergic mechanisms. His group has recently shown that cholinergic abnormalities exist in the peripheral microcirculation of CFS patients as demonstrated by enhanced skin vascular responses to graded doses of transdermally applied acetylcholine (ACh). To investigate the dynamics of this response further, the team measured time-dependent blood flow responses after a single dose of ACh and correlated these with activity levels of acetylcholinesterase (AChE) and buyrtylcholinesterase (BChE). Thirty patients (8M & 22F, mean age 43 years, range 18-57 years) who fulfilled the CDC criteria for CFS and 30 sex- and age-matched healthy controls were recruited. A blood sample was obtained for the measurement of AChE and BChE activity. Blood flow responses to ACh were measured on the volar aspect of the forearm using a scanning laser Doppler imager. Iontophoresis was used to transport the chemicals across the skin. Baseline skin perfusion was measured followed by iontophoresis of 1% ACh for 80 seconds using a 0.1 mA anodal current. After determining the peak blood flow response to ACh the subsequent recovery of blood flow was recorded. Two decay points were determined, T75 and T50, corresponding to the times taken for the blood flow to return to 75% and 50%, respectively, of the peak value to ACh minus the baseline value. The results showed that the peak hyperaemic response to ACh was not significantly different in the two groups, but the time for the ACh decay was significantly greater in the patients compared with controls for both T75 (13.7±11.3 vs. 8.9±3.7 minutes, p=0.03, respectively), and T50 (24.5±18.8 vs. 15.1±8.9 minutes, p=0.03, respectively). There were significant correlations between the blood flow recovery time and both AChE (positive correlation) and BChE (negative correlation) activity levels in healthy control subjects but not in CFS patients. AUTHORS' CONCLUSION: The novel findings of a prolonged action of ACh in the microvasculature and the lack of association between the rate of blood flow recovery and blood cholinergic enzyme levels in patients with CFS may provide further evidence of abnormal peripheral cholinergic activity in CFS. This may perhaps be related to an altered cholinesterase activity. The work was supported by MERGE (UK Charity 1080201)

Temporal patterns of cardiac autonomic response during head-up tilt in Chronic Fatigue Syndrome Kazuhiro Yoshiuchi et al. Department of Neurosciences, University of Medicine and Dentistry of New Jersey - New Jersey Medical School. Dr Yoshiuchi reiterated that, although a number of studies have reported that there are some alterations in cardiac autonomic nervous system in CFS, the results are not consistent. Two reasons for these discrepancies might be a) using a heterogeneous patient sample including those with orthostatic postural tachycardia (POTS), who have an obvious autonomic problem, and b) using FFT to analyze heart rate variability, which requires a stationary signal. To deal with these shortcomings, his group used the smoothed pseudo Wigner-Ville transformation (SPWVT) to evaluate autonomic function in CFS during orthostatic challenge. SPWVT has the advantage of providing instantaneous information about autonomic function from heart rate data in nonstable physiological conditions. Any subject with POTS was excluded, and so 18 CFS patients and 25 age-and gender-matched sedentary healthy controls were studied during supine rest and during the first 10 minutes after head-up tilt (HUT). While significant effects of postural change were found for all autonomic variables studied, only one variable showed a significant time x group interaction - instant centre frequency within low frequency regions (p=0.043). AUTHORS' CONCLUSION: Because the instant centre frequency provides information about sympatho-vagal balance, the data suggest that patients with CFS without POTS have a change in sympatho-vagal balance in favour of sympathetic predominance during HUT relative to healthy controls. This work was supported by NIH AI-32247

- ***Catecholamine responses to standardized stressors in Fibromyalgia and Chronic Fatigue Syndrome*** Daniel J. Clauw et al. University of Michigan, Ann Arbor, MI. Previous studies of the autonomic nervous system in FM and CFS have yielded conflicting results. Some studies have indicated sympathetic hyperactivity, whereas others have suggested hypoactivity. One of the most consistent findings across many studies, though, has been an attenuated response to stressors (e.g. hypoglycemia, exercise). To further explore this concept, Dr Clauw described work to concurrently examine FM and CFS subjects by exposing them to a standardized series of experimental stressors. Medication-free participants meeting established criteria for FM, CFS, or both were admitted for a two-day stay in the GCRC. Subjects with factors known to influence autonomic function were excluded. All individuals had a series of standardized stressors performed at the same time during the day, including pain testing, a cognitive

challenge, isometric handgrip, and a sub-maximal exercise test. Epinephrine and norepinephrine levels were assessed at pre-determined time points: pre-stressor, at least once during the stressor, and post-stressor. A total of 43 FM or CFS patients were compared with 44 controls. At nearly all time points throughout the study, the plasma levels of both epinephrine and norepinephrine were higher for the pooled patient group than that of the controls, with the norepinephrine differences nearly all being significant at the $p<0.01$ level. The exception was during peak exercise, where there was an attenuated rise in catecholamines in the patient group (norepinephrine 171% of baseline +/- 30 vs. 297% +/- 47, $p<0.02$) despite achieving similar workloads. At this point, and throughout the study, there were clear trends for the subjects with FM alone to have nearly normal increases in catecholamines in response to stressors, whereas those with CFS and FM were somewhat blunted, and subjects with CFS were more blunted. AUTHORS' CONCLUSION: The data suggest that individuals with FM and CFS have higher catecholamme levels (particularly norepinephrine) than controls, tested in a controlled environment while performing the same activities. The most potent stressor in this study was a sub-maximal exercise test; this was the only stressor robust enough to detect an attenuated response. The pattern of catecholamine responses was consistently different for CFS than FM, with individuals with CFS displaying attenuated responses. The degree of co-morbid CFS in previous studies of autonomic dysfunction may account for some of the differences seen in these studies.

Poster Presentations: Objectives and Conclusions (as given by the authors).

Rhinosinusitis symptoms are less common in those individuals with explained chronic fatigue than in those with unexplained chronic fatigue Alexander C. Chester et al. Georgetown University Medical Centre, Washington, DC.
AUTHORS' OBJECTIVE: Otolaryngologic surveys have documented chronic fatigue in those with rhinosinusitis and improvement of fatigue following functional endoscopic sinus surgery. Other studies note an increased prevalence of rhinosinusitis in patients with unexplained chronic fatigue. The following study was designed to determine if rhinosinusitis symptoms are as common in those with explained fatigue as it is in those with unexplained chronic fatigue.
AUTHORS' CONCLUSION: Those with unexplained chronic fatigue have substantially more rhinosinusitis symptoms than those with fatigue explained by a physical or mental illness, yet no difference is noted in the prevalence of symptoms often termed functional: gastrointestinal, sleep, and psychiatric complaints. Whether the unique relationship noted in this study between rhinosinusitis and unexplained chronic fatigue is related directly or indirectly to the cause or causes of UCF awaits further investigation.

Differences in activity limitations and participation restrictions between CFS and Fibromyalgia patients Jo Nijs et al. Faculty of Physical Education and Physiotherapy - Vrije Universiteit Brussel (VUB), Belgium.
AUTHORS' OBJECTIVE: This study aimed at comparing activity limitations and participation restrictions among FM and CFS patients, using the Chronic Fatigue Syndrome Activities and Participation Questionnaire (CFS-APQ). It was hypothesised that no major differences in activity limitations and participation restrictions exist between the two patients' groups, and consequently that the CFS-APQ might be useful for assessing part of the health status in FM patients as well. Therefore, the content validity and convergence validity of the CFS-APQ in FM patients were investigated.
AUTHORS' CONCLUSION: Except for 'sitting for 2 hours', these data indicate the lack of differences in the 21 activity limitations and 5 participation restrictions encompassed by the CFS-APQ between CFS and FM patients. Consequently, these results sustain the growing awareness of the great similarity between the two syndromes. The present data questions the disease specificity of the CFS-APQ for CFS, but suggests its applicability in 'the Chronic Pain-Fatigue Syndromes'. The latter was supported by the sufficient content and convergence validity of the CFS-APQ as seen in this sample of FM patients.

Assessment of risk factors in patients with undiagnosed chronic fatigue and pain Lucinda Bateman et al. Fatigue Consultation Clinic Salt Lake City, Utah.
AUTHORS' OBJECTIVE: To identify risk factors associated with, and possible subsets of, Fibromyalgia Syndrome (FMS), Chronic Fatigue Syndrome (CFS), combined FMS and CFS (FMS/CFS) or fatigue of other causes (OF) from a retrospective chart review of 325 consecutive patients presenting to a private practice Fatigue Consultation Clinic.
AUTHORS' CONCLUSION: Carefully screened chronic fatigue patients with no other obvious causes of fatigue are likely to meet criteria for either FMS or CFS. About one third of patients with CFS or FMS meet criteria for both syndromes. Mechanical head and neck trauma, either remote or recent, and IRS are predictors of meeting the FMS definition but not the CFS definition. In contrast, the patients with FMS only, unlike the CFS only patients, do not commonly report a history of infection one month prior to onset of symptoms. If patients have all these risk factors then they are likely to meet criteria for both FMS and CFS. The authors proposed that various types of neurologic injury other than viral or autoimmune, such as mechanical or metabolic injury, may be associated with the development of chronic myofascial pain, stiffness, neurogenic pain syndromes and tender points typical for FMS as opposed to the flu-like myalgias and arthralgias of CFS. FMS and CFS are useful terms used separately, even though they may describe subsets of a larger syndrome. Comparative data from patients who do not have chronic fatigue or pain are needed to draw additional conclusions.

A Clinical Evaluation of Gulf War Veterans with a Putative Deployment Related Neurologic Syndrome and Gulf War Era Controls PH Levine et al. The George Washington University Medical Centre (GWUMC), Washington, DC
AUTHORS' OBJECTIVE: To determine if neurologic findings can confirm the presence of a putative deployment-related Gulf War neurologic syndrome previously identified by factor analysis.
AUTHORS' CONCLUSION: Overall, this study did not uncover any specific deployment related objective neuro-opthalmologic abnormalities since the abnormal findings were evenly distributed between the symptomatic Gulf-deployed and non-Gulf deployed groups. However, the findings suggest an objective basis for the cluster of the four symptoms in the putative neurologic syndrome. Although statistical analysis suggested that the syndrome was related to deployment to the Persian Gulf because of the higher frequency of cases (2.4% of 10,423 compared to 0 45 % of 8,960 non-Gulf war deployed), the occasional cases in non-Gulf-deployed veterans may have a similar etiology. No specific etiology for this cluster of symptoms was

documented but suggested factors include multiple vaccines, with exposure to the Khamisiyah plume and deployment to Kuwait/Iraq as possible potentiating factors.

The phenomenology of post-exertional malaise Christopher R. Snell et al. University of the Pacific.
AUTHORS' OBJECTIVE: Symptom exacerbation following physical exertion is a common complaint among persons with Chronic Fatigue Syndrome, resulting in a post-exertional malaise that further constrains their often already limited activity levels. While post-exertional malaise remains a defining characteristic of CFS, this widely reported symptom is a source of some controversy. The purpose of this study was to further explore the effects of physical exertion on CFS symptomology from the perspective of those persons experiencing them.
AUTHORS' CONCLUSION: The results of this study indicate that, for at least some CFS patients, post-exertional malaise is a real and debilitating symptom. With 75% of the patients in this study taking three or more days to recover from a single bout of physical activity, the indication is also strong that CFS patients may exhibit non-normal responses to exercise. Various reported effects were inconsistent with what might normally be expected following exercise to exhaustion, even from sedentary and deconditioned individuals. For many patients in this study, the symptoms they experienced were wide-ranging, indicating a diverse pathology. It is interesting to note that despite patient heterogeneity often proving the bane of CFS research, numerous symptoms reported in this study were shared by multiple participants. The debilitating effects experienced by these patients go a long way toward explaining activity avoidance in CFS and highlight the need for special consideration when prescribing exercise as therapy for CFS patients.

Chronic fatigue syndrome: sudden onset does not occur randomly over the course of the year Alison C. Bested et al. Sunnybrook and Women's College Hospital, Environmental Health Clinic, Toronto, Canada.
AUTHORS' OBJECTIVE: To determine if sudden onset of Chronic Fatigue Syndrome is associated with random onset over the course of the year.
AUTHORS' CONCLUSION: These results show that in CFS patients who report sudden onset of illness, there is a non-random pattern of onset. The majority of cases occurred during the influenza season, with high occurrences in both September and March, classically the beginning and end of the flu period in the Northern Hemisphere. The authors' definition of sudden onset was within one month, much less strict than that of previous investigators (e.g,, Zhang 2000, Jason 2001). These results suggest a viral connection in a subset of CFS patients and conflict with a somatoform disorder.

Psychometric properties of the Chronic Fatigue Syndrome activities and participation questionnaire Jo Nijs et al. Faculty of Physical Education and Physiotherapy - Vrije Universiteit Brussel (VUB), Belgium.
AUTHORS' OBJECTIVE: Identifying patients' activity limitations is crucial for teaching CFS patients to effectively manage their activity level ("pacing"). The time-consuming interpretation of generic measures like the Medical Outcomes Short Form 36 Health Status Survey (MOS SF-36) hinders its routine application in physical therapy practice. Therefore, a quick and disease-specific questionnaire to assess activity limitations and participation restrictions in patients with CFS was recently constructed. In this study, the reliability and the congruence validity of this measure, named the CFS-Activities and Participation Questionnaire (CFS-APQ), were investigated.
AUTHORS' CONCLUSION: The items of the CFS-APQ have been found to have good internal consistency, and these results substantiate the congruence validity of the scores obtained with this new questionnaire. Consequently, the CFS-APQ appears to be a reliable and valid measure that should aid physical therapists in the baseline and outcome assessment, as well as deciding upon a treatment plan for CFS patients.

Ratio of ribonuclease L isoforms (37 kDa/83 kDa) as a new diagnostic tool in the Chronic Fatigue Syndrome. K P Tiev et al. Service de Medecine Interne, Hopital Saint Antoine, 184 rue du Faubourg Saint Antoine, 75571 Paris Cedex 12.
AUTHORS' OBJECTIVE: CFS is a disorder characterized by debilitating fatigue associated with immunological abnormalities. The aetiology remains unclear. However, viral infections frequently occur before the onset of CFS. Dysfunction of the 2-5A/RNase L antiviral pathway in patients with Chronic Fatigue Syndrome has been reported by several groups. In particular, a 37 kDa 2-5A binding polypeptide has been identified in 88% of CFS compared with only 28% of healthy control subjects and the ratio of two isoforms of RNase L (37kDa/83kDa) has been proposed as a potential biochemical marker of CFS. The aim of this study was to evaluate the discriminating value of that test.
AUTHORS' CONCLUSION: These data were challenged by Gow et al. (Infect. Dis 2001; 33: 2080-2081) who suggested that the high activity of the RNase L found in CFS patients was just a coincidence and reflected probably an ongoing viral infection. Indeed, RT- PCR analysis showed that RNase L mRNA level did not differ between a CFS group and a healthy volunteer group. However, these data are not

contradictory, since Gow et al. did not take into consideration the fact that the accumulation of a 37kDa isoform of RNase L, as described here and as reported by De Merleir et al. may result from proteolysis of RNase L independently of RNase L mRNA level. In CFS, the accumulation of fragments with molecular weight of 37 kDa could be due to an increased proteolytic activity in PBMC extracts. The results confirm that a ratio of RNase L isoforms (37 kDa/83 kDa) higher than 0.4 seems to be sensitive to screen CFS patients in absence of any known infection. Additional large studies, however, are required to define the effective importance of this diagnostic test and its clinical benefit. The stability of this high level ratio of RNase L isoform in a CFS group compared to a group of healthy volunteers remains to demonstrated.

Immunophenotyping predictive of mycoplasma infection in patients with Chronic Fatigue Syndrome? Nijs Jo et al. Faculty of Physical Education and Physiotherapy - Vrije Universiteit Brussel (VUB), Belgium.
AUTHORS' OBJECTIVE: An impaired immune system and opportunistic infections are considered important characteristics in the pathophysiology of CFS. To the authors' knowledge, the possible effects of *Mycoplasma* species on immune cells in CFS patients have not been examined. Therefore, they examined CFS patients with or without mycoplasmal infection(s) and healthy volunteers to see if certain immune patterns were characteristic of chronic infections in these patients.
AUTHORS' CONCLUSION: These data confirm earlier reports on immune activation among CFS patients, but this does not appear to be specific for mycoplasma-infected CFS patients. Indeed, both the CFS patients with or without evidence of a *Mycoplasma* species infection presented with significantly elevated CD25+ cells, suggesting an immune response against another pathogen in the *Mycoplasma*- negative patients. Immune activation appears to be less controlled in Mycoplasma-infected CFS patients in comparison to *Mycoplasma* negative CFS patients.

Cytokine evaluation in Chronic Fatigue Syndrome patients in Japan. Takako Jhodoi et al. Department of Child Development, Kumamoto University School of Medicine, Kumamoto, Japan.
AUTHORS' OBJECTIVE: Currently, there is no established therapy for CFS. Recently, the authors obtained information which suggested effectiveness of low dose gamma-globulin therapy for CFS patients. Therefore, the authors treated the CFS patients in Japan with low dose gamma-globulin. In this study, they also examined the behaviour of cytokine production patterns in parallel with the study.
AUTHORS' CONCLUSION: This group of patients is too small, but the results suggest treatment with intravenous low dose gamma-globulin is effective for CFS. The authors emphasize that low dose gamma-globulin therapy might be considered as a possible therapy for CFS, especially for those with low TGF β-1.

Increased neutrophil apoptosis in Chronic Fatigue Syndrome Gwen Kennedy et al. Vascular Diseases Research Unit, University Department of Medicine, Ninewells Hospital & Medical School, Dundee, Scotland, UK, DD1 9SY.
AUTHORS' OBJECTIVE: Patients with CFS have symptoms that are indicative of an underlying viral or toxic illness. In support of this there have been various reports of immunological disturbances and viral infections in the disease and many CFS patients complain of recurrent and/or persisting infections. Apoptosis is the term used when a cell dies following an ordered and distinct pathway. Deviation from the normal mechanism of apoptosis or alterations in the triggers or signalling of the process can result in disease. Neutrophils represent 50-60% of the total circulating white blood cells and are fundamental in the functioning of an intact immune system. The role of the neutrophil is to destroy infectious agents. Cytokines and growth factors are involved in the processes of apoptosis and inflammation, e.g. tumour necrosis factor (TNF) and transforming growth factor-β1 (TGF-beta-1). They both have also been implicated in the pathogenesis of CFS. TNF receptor-I (TNF-RI) is also know as a death receptor and the binding of TNF-alpha to TNF-RI triggers the cell to undergo apoptosis. The aim of this study was to investigate the level of apoptosis in neutrophils and the plasma levels of TGF-β1 in patients with CFS and age and sex-matched healthy control subjects.
AUTHORS' CONCLUSION: We have shown that patients with CFS also have increased neutrophil apoptosis and higher levels of TGF-β1. We suggest that increased neutrophil apoptosis and inhibition of transmigration of neutrophils by higher TGF-β1 levels may be indicative of a persistent viral infection or a toxic state giving rise to many of the symptoms which characterise CFS. It might also be that increased apoptosis merely reflects a quicker turnover of neutrophils in this condition but either way the data presented here provide convincing evidence that many patients with CFS have an underlying detectable abnormality. Results: www.meresearch.org.uk/research/

In vivo and in vitro abnormal cellular reactivity to Candida albicans in patients with CFS G.J.N. Cozon et al. Immunologie, Service des maladies infectieuses Hopital de la Croix Rousse, Lyon, France.

AUTHORS' OBJECTIVE: Etiopathogeny of CFS is unknown and may be the results of multifactorial causes. Chronic brucellosis induces chronic fatigue and may be considered as a natural model for CFS of known etiology. In this disease, skin reaction to Brucella antigen can exacerbate symptoms within 3 days. In some CFS patients suspected for immediate hypersensitivity to *Candida albicans*, the authors noticed a delayed exacerbation of fatigue when testing them with *C. albicans* antigen. These observations suggested to the authors an abnormal cellular reactivity to *C. albicans*. In the present study they explored cellular immunity to *C. albicans* in patients with CFS.
AUTHORS' CONCLUSION: The present study confirms that a complete clinical and biological check up is necessary to eliminate a well-defined cause of fatigue. In addition, quite half of the patients have an atopic background. Moreover the present study shows that an abnormal delayed reactivity to *C. albicans* was detected in quite 60% of the patients. This abnormal reactivity was characterized by abnormal systemic reactions in response to a skin test with *C. albicans* and by high levels of circulating T cells that were activated in the presence of *C. albicans* antigen for 24 hours. Subjective systemic reactions were always confirmed by an increased excretion of neopterin within 3 days after the skin test to *C. albicans*. The cause to effect relation between skin test to *C. albicans* and systemic reaction suggests a role for this antigen in the pathogenesis of chronic fatigue in a subpopulation of CFS patients. As *C. albicans* is an ubiquitous yeast of mucosal surface the authors hypothesize that in these patients *C. albicans* may activate an important fraction of T cells. This activation may induce cytokine production such as interferon-y that induce neopterin production by macrophages. Interferon-gamma may act on the central nervous system to decrease the threshold of fatigability. Preliminary results show that treatment of these patients with probiotics and low-sugar diet can improve their life quality. More studies are necessary to validate this hypothesis. Other fatigue factors such as depression and sleep disturbance have also to be considered in the treatment of CFS patients.

Correlation of sleep parameters to immunological variables in Chronic Fatigue Syndrome Eike Van Hoof et al. Department of Human Physiology - Vrije Universiteit Brussel - Belgium
AUTHORS' OBJECTIVE: Several researchers showed reduced sleep efficiency, a reduction of REM sleep, a longer sleep initiation, lower percentage of stage 4 sleep, and alpha-wave intrusion as common sleep problems in CFS. Although there is a reasonable amount of data supporting the influence of immune parameters on sleep variables, no effort has yet been made to unravel possible causal relationships. In this study, correlations and a regression tree were investigated in order to indicate possible causal relationships.
AUTHORS' CONCLUSION: The existence of sleep latency problems and other sleep disturbances are validated as already suggested by several authors. Overall, the results of the correlations and the regression tree suggest a major role of immune parameters in sleep. It could be suggested that immune alterations increase the percentage of alpha-intrusion due to anti-infectious activity.

Chlamydia pneumoniae and deregulation of the 2.5A synthetase RNase L pathway in CFS patients Jo Nijs et al. Department of Human Physiology - Faculty of Physical Education and Physiotherapy, Vrije Universiteit Brussel (VUB), Belgium.
AUTHORS' OBJECTIVE: *Chlamydia pneumoniae* are intracellular prokaryotic cells, frequently associated with fatigue in infected patients and previously suggested to contribute to patients' morbidity in subsets of patients with CFS. This group has recently revealed an association between Mycoplasma infection and dysregulation of the 2',5' oligoadenylate (2.5A) synthetase RNase L antiviral pathway in subsets of patients with CFS. Dysregulation of the 2.5A synthetase RNase L pathway implicates an impaired cellular immune response, consequently increasing the risk of intracellular pathogens like *C. pneumoniae*. Likewise, TNF-alpha is believed to be of great importance for cell-mediated immunity against *C. pneumoniae*. CFS patients with a dysregulated 2.5A synthetase RNase L antiviral pathway and associated TNF-a converting enzyme (TACE)-degradation by elastase are likely to be more vulnerable to chronic *C. pneumoniae* infection. This study is therefore aimed at examining possible interactions between the dysregulation of the 2.5A synthetase RNase L antiviral pathway and *C. pneumoniae* in patients with CFS.
AUTHORS' CONCLUSION: These results do not support any association between the dysregulation of 2.5A synthetase RNase L antiviral pathway and *C. pneumoniae* infection in patients with CFS. As no attempt was made to control for bias originating from Mycoplasma infection, these results should be interpreted with some caution. Indeed, 50 out of 67 (74.6%) *C. pneumoniae*-infected CFS patients had evidence of a deregulated 2.5A synthetase RNase L pathway, characterised by a RNase L ratio > 2. Future research should therefore re-address these possible interactions using Real Time PCR for the detection of both *Chlamydia* and Mycoplasma species.

Ribonuclease L proteolysis in peripheral blood mononuclear cells of Chronic Fatigue Syndrome patients. E. Demettre et al. Lebleu Universite Montpellier, Montpellier, France/University of Brussel, Brussels Belgium.

AUTHORS' OBJECTIVE: Chronic fatigue syndrome (CFS) is associated with long-lasting debilitating fatigue, impairment of neurocognitive functions and flu-like symptoms, and there is no biochemical diagnostic test for this disease. The accumulation in peripheral blood mononuclear cells (PBMC) of a 37 kDa 2-5A binding polypeptide might become the basis of a diagnostic marker (De Meirleir et al. Am. J. Med. 108 (2000) 99-105) allowing discrimination of CFS from diseases with overlapping symptoms, and tracking of disease evolution.
AUTHORS' CONCLUSION: This low molecular weight 2-5A binding polypeptide is a truncated form of RNase L, generated by an increased proteolytic activity in CFS PBMC extracts which leads to the accumulation of two major fragments. The 37 kDa 2-5A binding fragment includes the N-terminal end of RNase L and extends beyond the 2-5A binding site. The 30 kDa fragment starts in the protein kinase homology domain and includes the RNase L catalytic site. RNase L remains fully active and 2-5A dependent when degraded into its 30 kDa and 37 kDa fragments by CFS PBMC proteases or by purified human leucocyte elastase. This 2-5A dependent nuclease activity could possibly be provided by an association of these digestion products. RNase L truncation could lead to dysregulation which in turn could lead to the degradation of cellular mRNAs which are not normal targets of native RNase L. Supported by CNRS, CFIDS America and RED Laboratories.

Impaired natural immunity and heightened lymphocyte activation relate to greater disruptions in patients with CFS M.H. Antoni et al. University of Miami.
AUTHORS' OBJECTIVE: The present study tested a theoretical model that proposes that the fatigue-related symptoms of CFS may be determined in part by a combination of poor natural immunity (natural killer cell activity) and a state of overactivation of specific lymphocyte subsets, possibly reflecting a dominance ofTh2 cytokines over Th1 cytokines.
AUTHORS' CONCLUSION: These analyses underscore the importance of characterizing the dual immunologic picture of CFS as theorized in the authors' conceptual model: one of low natural killer cell activity and high activation state of other aspects of the immune system.

Atopy prevalence in Chronic Fatigue Syndrome Ferre L et al. Internal Medicine, Allergy Services. Hospital Vail d'Hebron, Delfos Medical Centre. Barcelona. Spain.
AUTHORS' OBJECTIVE: Chronic fatigue syndrome is an entity that imposes a severe disability on CFS patients in such diverse areas as fatigue, muscular symptoms, weakness, headache, sleep disturbances and neurocognitive dysfunction. Different hypotheses exist on the etiopathogenesis of the CFS, among them the immunologic. The aim of the study was to evaluate whether or not an allergic sensitization is higher in patients with CFS compared with the general population.
AUTHORS' CONCLUSION: There were no statistically significant differences among Chronic Fatigue Syndrome patients and controls ($p>0.05$).

Interferon-induced RNase L and PKR antiviral pathway activation in Chronic Fatigue Syndrome Gow JW et al. Glasgow University Departments of Neurology, Immunology and Pathology, Glasgow G12 8QQ, Scotland, UK.
AUTHORS' OBJECTIVE: To investigate whether an assay of interferon-induced RNase L and PKR antiviral pathway activation could be used as a diagnostic test for Chronic Fatigue Syndrome.
AUTHORS' CONCLUSION: If activation of the antiviral pathways is observed in patients then the data suggests that the patient is suffering from a current or recent infection - not that the patient has CFS. Therefore, the authors believe that their data strongly suggests that assay of the RNase L/PKR antiviral pathways is unlikely to form a basis for a diagnostic test for CFS. In addition, drug treatment aimed at these pathways is unlikely to be of clinical benefit to patients with CFS. (Gow, et al, CID; 2001; 33:2080-1). We acknowledge the kind financial support of the ME Association and the Barclay Trust.

Fractal analysis of heart rate variability during postural challenge in CFS: effect of maximal exercise Dane B. Cook et al. Department of Neurosciences and Radiology, University of Medicine and Dentistry of New Jersey - New Jersey Medical School.
AUTHORS' OBJECTIVE: Chronic fatigue syndrome has been reported to be associated with orthostatic intolerance. If autonomic nervous system abnormalities are present, fatiguing exercise will exaggerate the reactivity of the autonomic nervous system to the postural change from lying to standing. Therefore, the authors compared autonomic function in CFS during orthostatic challenge with that in healthy controls before and after a maximal exercise test by analyzing heart rate variability. A number of studies have reported that heart rate variability includes not only regular periodic components, but also a periodic or fractal component. Therefore, we used the coarse graining spectral analysis to evaluate both harmonic and fractal components of heart rate variability.
AUTHORS' CONCLUSION: There are some differences in autonomic function between CFS patients and healthy people, and exercise exaggerated differences in the reactivity to postural change between the two groups including both periodic and fractal components

of heart rate variability. Work supported by NIH AI-32247.

Abnormal breathing adjustments to postural stress in Chronic Fatigue Syndrome Arnold Peckerman et al. Centre for the Study of War-Related Illnesses, VA Medical Centre, East Orange, NJ.
AUTHORS' OBJECTIVE: The authors hypothesized that ineffective use of respiratory muscles may be contributing to worsening of symptoms in the standing position in CFS patients. The present study examined this hypothesis by compartmentalizing the breathing motion into the chest and abdominal components to assess relative recruitment of intercostal and diaphragmatic respiratory muscle groups.
AUTHORS' CONCLUSION: Based on our preliminary data, CFS patients have a significant increase in recruitment of the chest muscles in the standing position. This was associated with an increase in light headedness in the standing position in the CFS patients, which was proportional to the increase in minute ventilation but was excessive relative to the degree of decline in end-tidal C02. The smaller than expected decline in end-tidal C02 relative to the increase in minute ventilation might therefore be indicative of increased CO2 production due to increased utilization of intercostal muscles. These data support the hypothesis that worsening of symptoms commonly reported by the CFS patients during standing activities may in part be attributable to inefficient utilization of respiratory muscles when standing. Further studies of breathing during passive upright posture, not involving the use postural muscles, would be needed to determine whether the abnormal adjustments observed in the study were due to posture itself or to the greater energy expenditure that occurs during active standing.

Renin-aldosterone axis and orthostatic hypotension in patients with CFS Theodore C. Friedman et al. University and Cedars-Sinai Medical Centre, Los Angeles, CA.
AUTHORS' OBJECTIVE: The authors hypothesized that the etiology of a subgroup of patients with CFS is reduced mineralocorticoid activity and subsequent reduction of blood volume, resulting in impaired cerebral blood flow (CBF). The underlying defect may be autonomic nervous system dysfunction and/or a primary adrenal defect. Therefore, the primary objective of this study was to characterize the renin-aldosterone axis in patients with CFS to identify this subset of CFS patients.
AUTHORS' CONCLUSION: The authors conclude that a large percentage of patients with CFS have defects of their renin-aldosterone axis. It was proposed that patients with CFS and impaired mineralocorticoid activity represent a discrete, previously unrecognized disease entity, with its own pathophysiology and functional characteristics, and that these patients will benefit from unique treatment options.

Gender, exercise capacity, and Chronic Fatigue Syndrome J. Mark VanNess et al. University of the Pacific.
AUTHORS' OBJECTIVE: More women than men are diagnosed with CFS. Inevitably this often leads to unequal gender distribution among research subjects. This can be particularly problematic when exercise capacity is used as a dependent variable and gender data are pooled. Oxygen uptake is a critical measure of exercise capacity and in women this is usually lower than in men. When not controlled for, this gender difference may confound research results. The purpose of this study was to compare the responses to exercise of male and female CFS patients while also controlling for age and exercise capacity.
AUTHORS' CONCLUSION: In using oxygen uptake during exercise to quantify functional impairment, the AMA makes no distinctions between genders. That the women in this study achieved a peak V02 closer to their maximal predicted values inevitably raises the issue of possible gender bias in disability classification. It is possible that these results could be explained by fitness factors unrelated to CFS. BMI for the women was within the good fitness zone (18.0-24.9), while BMI for the males was in the marginal zone (25.0-27.7), between good fitness and high risk (>27.8). The significantly lower increase in systolic BP among the women might also suggest higher fitness levels compared to the males. A further explanation for these results may centre on male/female hormonal differences and endocrine function during exercise. Exercise mediated endocrinological abnormalities that may differentiate between CFS patients and healthy controls could also vary as a function of gender within the CFS population. Reasons for the observed differences notwithstanding, these results illustrate the importance of considering gender as a variable when designing and conducting CFS research.

Submaximal exercise testing in patients with Fibromyalgia, Chronic Fatigue Syndrome, and controls Kirsten Ambrose et al. University of Michigan, Ann Arbor, MI.
AUTHORS' OBJECTIVE: To evaluate physical performance, and heart rate (HR) and blood pressure (BP) responses to sub-maximal cycle ergometry testing in patients and controls.
AUTHORS' CONCLUSION: Physical performance and physiological responses were similar between the patients and controls, with exceptions in resting and low-level exercise diastolic BP responses. These findings are contrary to the perceived notion that these patient groups consistently exhibit diminished exercise performance and/or a blunted heart rate response relative

to controls. As well, they suggest that the heterogeneity of these patient populations may lead to broad generalizations about their exercise capabilities when, in fact, particular subgroups of patients may perform differently than others with respect to exercise testing.

Heart rate variability and autonomic function in Fibromyalgia and Chronic Fatigue Syndrome Kirsten Ambrose et al. Washington University, St. Louis, MO.
AUTHORS' OBJECTIVE: Autonomic nervous system abnormalities are believed to be associated with chronic multisymptom illness (CMI) such as Fibromyalgia (FM), CFS and Gulf War Veteran's Illnesses (GWVI). Decreased heart rate variability (HRV), a marker for abnormal cardiac autonomic modulation, has been reported in female FM patients compared to healthy controls. Little is known about HRV in other CMI patients or in male CMI patients.
AUTHORS' CONCLUSION: This study replicates the previous findings of altered HRV in female FM patients, and extends these findings to female CFS and GWVI subjects. However, males with these conditions did not demonstrate the same findings, although male and female controls did not differ. Although women more commonly develop CMI then men, gender effects must be considered when analyzing these mechanisms in CMI.

Ampligen® treatment of patients with CFS under an expanded access program David R. Strayer, and AMP 511 investigators. Hemispherx Biopharma Inc., Philadelphia, PA.
AUTHORS' OBJECTIVE: To review safety and physical performance/cognitive clinical endpoints including Karnofsky Performance Scores and Cognitive Function data derived from an expanded access treatment protocol using Ampligen® for treatment of CFS.
AUTHORS' CONCLUSION: An analysis of data from an expanded access treatment protocol using Ampligen in CFS shows significant improvements in physical performance, cognitive function, vitality, and physical activity. The treatment was generally well tolerated and the majority of patients continued treatment beyond 24 weeks.

Chronic Fatigue Syndrome: an assessment of dietary/herbal supplement intake by patients in a clinical setting Alan C. Logan et al. CAM Research Consulting, Mahwah, NJ.
AUTHORS' OBJECTIVE: To determine the frequency and quantity of dietary/herbal supplement consumption by CFS patients in a clinical setting.
AUTHORS' CONCLUSION: In this clinical setting, CFS patients report the frequent consumption of a wide variety of dietary/herbal supplements. With such a large variation in the types of remedies used by CFS patients, the potential for drug-supplement interaction is high. Most CFS patients report supplement use to doctors. Dietary/herbal supplements have been the subject of very limited quality research in the area of CFS and more research is necessary in this area to determine which, if any, supplements have therapeutic value in CFS.

Chronic Fatigue Syndrome patients in a clinical setting frequently report self-directed mind/body interventions. Alison C. Bested et al. Sunnybrook and Women's College Hospital, Environmental Health Clinic, Toronto, Canada.
AUTHORS' OBJECTIVE: To investigate the use of Mind/Body techniques as reported by CFS patients in a tertiary setting.
AUTHORS' CONCLUSION: CFS patients frequently use Mind/Body medicine and those patients who use these various techniques often report them as somewhat or very helpful. Despite high patient utilization in an effort to manage the symptoms of CFS, Mind/Body techniques remain under-researched in the area of CFS. Further research is necessary to determine the psychophysiological benefits of Mind/Body techniques in CFS.

Administration of Transfer Factor for Human Herpesvirus 6 (HHV-6) in Patients with Chronic Fatigue Syndrome and HHV-6 Viremia Joseph H. Brewer et al. Plaza Internal Medicine-Infectious Disease and Saint Luke's Hospital (Infectious Diseases) Kansas City, Missouri.
AUTHORS' OBJECTIVE: Chronic fatigue syndrome (CFS) has been associated with active HHV-6 infection. CFS has also been associated with immune dysfunction, especially with regard to natural killer (NK) cell function. Since the active infection may be playing a key role in CFS and the associated immune dysfunction, the authors wanted to study the effects of a transfer factor (TF) with activity for HHV-6 in CFS patients.
AUTHORS' CONCLUSION: Patients with CFS and documented HHV-6 viraemia improve both symptomatically and immunologically (NK function) after administration of a TF preparation with activity for HHV-6. Immune enhancers such as the TF studied herein, may be important in the treatment of CFS and the associated active HHV-6 infection.

Dietary modifications, food sensitivities and migraine headaches reported by CFS patients Alan C. Logan et al. CAM Research Consulting, Mahwah, NJ.
AUTHORS' OBJECTIVE: To investigate the frequency of self-directed, unspecified dietary modifications, food

sensitivity and pre-illness migraines as reported by CFS patients in a clinical setting.
AUTHORS' CONCLUSION: These results suggest that CFS patients frequently attempt self-directed dietary modifications in an effort to manage symptoms and that such efforts are most often somewhat or very helpful. Food sensitivities appear to be a result of CFS illness onset and may exacerbate symptoms in certain patients. Pre-CFS migraines do not appear to be a factor in food sensitivity reporting. The evidence related to food intolerances and CFS is scant, and further research may provide clues as to what, if any, specific alteration(s) in the diet may be helpful in managing CFS symptoms.

Moxibustion on "shitsumin" may reduce fatigue level of patients with Chronic Fatigue Syndrome Takeo Madarame et al. Institute of Oriental Medicine and Institute of Geriatrics, Tokyo Women's Medical University, School of Medicine.
AUTHORS' OBJECTIVE: There is no specific treatment for CFS and many kinds of intervention are necessary to improve fatigue. The authors have treated patients with CFS by the combination therapy with Kampo medicine, which is a Japanese traditional herbal medicine, and psychotropic drugs. Some of the patients improved completely but most of the patients improved incompletely, without change or even aggravated by the combination therapy. In this study, we applied moxibustion on "Shitsumin" and investigated the effect of moxibustion for patients with CFS.
AUTHORS' CONCLUSION: Moxibustion on "Shitsumin" is one of the effective treatments for patients with CFS.

Eye movement desensitization in Fibromyalgia: a pilot study Fred Friedberg. State University of New York at Stony Brook.
AUTHORS' OBJECTIVE: This study sought to assess the effects of a two-session Eye Movement Desensitization (EMD) treatment on the symptoms of pain, stress, fatigue, and associated functional limitations in Fibromyalgia..
AUTHORS' CONCLUSION: EMD in this preliminary, uncontrolled study yielded few statistically significant findings, but generally larger effect sizes with fewer sessions than those typically reported in cognitive-behavioural treatment studies for Fibromyalgia. Most subjects could do unsupervised self-EMD without negative effects. Because EMD produced a somewhat automatic relaxation response with minimal client participation, it may be especially useful when standard relaxation techniques fail.

Treatment with staphylococcus toxoid in FM/CFS - antibody levels are related to clinical improvement Olof Zachrisson et al. From Institute of Clinical Neuroscience, Goteborg University.
AUTHORS' OBJECTIVE:. The authors conducted a 6-month randomized controlled trial on the staphylococcus toxoid vaccine Staphypan Bema (SB) in 100 female patients with both Fibromyalgia (FM) and CFS. Treatment included weekly injections containing 0.1 ml, 0.2 ml, 0.3 ml, 0.4 ml, 0.6 ml, 0.8 ml, 0.9 ml, 1.0 ml SB or placebo (coloured sterile water), followed by booster doses given 4-weekly until endpoint. The aim of the present study was to evaluate, in a subset of participants, the antibody status against staphylococcal antigens (extracellular toxins or enzymes, cell wall components, enterotoxins) at baseline and at endpoint, and to explore the relation between serological and clinical response.
AUTHORS' CONCLUSION:. This explorative study has shown that repeated injections in FM/CFS patients with the Staphypan Berna vaccine caused a serological response to several staphylococcal antigens, particularly to certain extracellular toxins and enzymes, and that this response is related to the clinical outcome of treatment. Serum antibody determinations may be used in the future to monitor treatment with immunomodulating agents such as bacterial components.

A rating scale for Fibromyalgia and Chronic Fatigue Syndrome (the FibroFatigue scale) Olof Zachrisson et al. Institute of Clinical Neuroscience, Goteborg University, Sweden.
AUTHORS' OBJECTIVE: To construct an observer's rating scale sensitive to change for measuring severity and treatment outcome in Fibromyalgia (FM) and CFS patients.
AUTHORS' CONCLUSION: The FibroFatigue scale seems to be a reliable and valid measuring instrument with capacity to monitor symptom severity and change during treatment of FM/CFS patients. Further studies are, however, needed to investigate the usefulness of the scale.

Magnesium and vitamin D status in female patients with CFS, Fibromyalgia or autonomic dysfunction Herlindis Wynants et al. Department of Internal Medicine, University Hospital Antwerp, Belgium.
AUTHORS' OBJECTIVE: Patients suffering from CFS, Fibromyalgia or autonomic dysfunction often have complaints of neuromuscular irritability and muscle weakness, both common features in magnesium and vitamin D deficiency. In a population of patients with CFS, Fibromyalgia or autonomic dysfunction, magnesium and vitamin D levels were studied.
AUTHORS' CONCLUSION: In all three patient groups studied, individuals with a deficiency of vitamin D were found. A considerable amount of patients belonging to the three groups also showed a low content of magnesium in erythrocytes and a decreased magnesiuria, suggesting a magnesium deficiency. The authors conclude that determination of 25-OH-vitamin D, red blood cell magnesium and magnesiuria is easy and

useful in these syndromes in order to prescribe the supplements needed.

Application of a Cognitive Function Index (CFI) For CFS Patients: Relationship of Brain Abnormalities to Cognitive Function G. Lange et al. Depts of Psychiatry, Neurology, New Jersey Medical School UMDNJ, and Centre for The Study of Unexplained Illness, Orange VA, NJ.
AUTHORS' OBJECTIVE: To show that significant differences in overall cognitive function exist between CFS groups and Controls that showed evidence of brain abnormalities on magnetic resonance imaging (MRI).
AUTHORS' CONCLUSION: The presence of brain abnormalities seems to have an effect on overall cognitive function as assessed with the CFI. Subjects with brain abnormalities (consisting of CFS and Control subjects) are significantly more impaired on the CFI scale than those without.

Effect of exercise on neurocognitive function in CFS patients Dane B. Cook et al. CFS CRC, Department of Neuroscience and Department of Radiology, University of Medicine and Dentistry of New Jersey, Newark, NJ.
AUTHORS' OBJECTIVE: Patients with CFS suffer from impairment in thought concentration, attention span and short-term memory, referred to as neurocognitive symptoms. These symptoms are reported to be exacerbated following physical exertion. However, recent reports suggest that CFS patients can perform a short, maximal bout of exercise without significant deficits in cognitive performance. The purpose of this study was to determine the effect of longer duration submaximal exercise on cognitive performance in patients with CFS. The authors chose an exercise challenge of moderate intensity that would be more in line with the normal activities of CFS patients and also employed a no-exercise control group to more clearly determine the effect of "exercise" on cognitive performance.
AUTHORS' CONCLUSION: Based on preliminary data, CFS patients show subtle baseline cognitive deficits. Importantly, cognitive performance is not made worse by light exercise. Additionally, light exercise may help to improve short-term memory in CFS. Clarification of the relationship between exercise and cognitive performance in CFS patients may be useful in studies of prognosis and may help define subsets of patients who may benefit from exercise. Work supported by NIH AI-32247.

Elevated nitric oxide/peroxynitrite theory of Chronic Fatigue Syndrome, Fibromyalgia and related conditions Martin L. Pall and Iva Smimova. School of Molecular Biosciences, Washington State University, Pullman WA 99164-4660.
AUTHORS' OBJECTIVE: To outline the proposed mechanism of the elevated nitric oxide/peroxynitrite theory of CFS, Fibromyalgia (FM) and related conditions, review the literature supporting it and to present data in 4 critical areas relating to this theory.
AUTHORS' CONCLUSION: Fourteen different types of data provide support for the elevated nitric oxide/peroxynitrite theory of CFS etiology (1-4) and substantial support for this theory has also been reported for the related conditions FM (5), multiple chemical sensitivity (6,7) and posttraumatic stress disorder (5). To the authors' knowledge this is the only etiologic theory providing explanations for the multiple overlaps among these conditions that have been reported by several different research laboratories. Cases of each of these conditions are reported to be often preceded by and putatively induced by a short term stressor, most commonly infection in the case of CFS and physical trauma in the case of FM, and each of these stressors are known to produce increases in nitric oxide (1,5). Nitric oxide reacts with superoxide to form the potent oxidant, peroxynitrite. There are multiple known biochemical mechanisms by which peroxynitrite can act to increase the levels of both of its precursors, nitric oxide and superoxide which can react, in turn to form more peroxynitrite. It is this biochemical vicious cycle which is proposed to be responsible for the chronic nature of these conditions, albeit with somewhat different tissue distributions in the different conditions. The 14 types of data supporting this theory of CFS and 7 different types of data supporting this theory of FM were outlined while focusing specifically on four of the CFS studies. Evidence was presented that vitamin B-12 injections, which have been widely used to treat CFS, FM and related conditions may be therapeutically useful because B-12 in the form of hydroxocobalamin is a potent nitric oxide scavenger. Serum studies were presented showing that the levels of citrulline, the co-product of nitric oxide synthases, are elevated in the sera of CFS patients when compared with controls and that the citrulline levels also correlate with CFS severity. In addition, protein carbonyl levels, a marker of oxidative damage, are also elevated in CFS sera, as expected if the potent oxidant peroxynitrite is elevated. A drug reported to cure proposed animal models of CFS, thiacetarsamide, is a scavenger of both nitric oxide and peroxynitrite.
References: 1. Pall, ML. Med Hypoth 2000; 54: 115-125. 2. Pall ML. J Chronic Fatigue Syndr 2000; 7(4): 45-58. 3. Pall ML. J Chronic Fatigue Syndr. 2001; 8(2): 39-44. 4. Pall ML. Med Hypoth 2001; 57: 139-145. 5. Pall ML. J Chronic Fatigue Syndr, in press. 6. Pall ML and Satterlee JD. Ann NY Acad Sci 2001; 933: 323-329. 7. Pall ML FASEB J 2002; in press.

Gene expression profiling of patients with Chronic Fatigue Syndrome and healthy controls using cDNA

microarray technology H. Ojaniemi et al. Karolinska Institutet at Huddinge University hospital, Stockholm.
AUTHORS' OBJECTIVE: To evaluate differences in peripheral blood gene expression profiles between twenty patients fulfilling criteria for CFS and twenty age and sex matched healthy controls using glass microarrays.
AUTHORS' CONCLUSION: See presentation Vernon et al. (above).

Chronic Fatigue Syndrome: a central fatigue disorder? E.Georgiades et al. Centre for Exercise Science and Medicine, Institute of Biomedical and Life Sciences, University of Glasgow, Glasgow, UK.
AUTHORS' OBJECTIVE: - To determine the extent of involvement of both peripheral and central mechanisms of fatigue in the aetiology of CFS by examining cardiopulmonary and metabolic responses, and the profiles of selected serotoninergic and dopaminergic modulators during symptom-limited exercise and subsequent recovery in CFS, relative to those of matched sedentary controls.
AUTHORS' CONCLUSION: The findings of the present study support previous reports of impaired exercise tolerance, concurrent with exacerbated effort perception in CFS. However, the heterogeneity in the cardiovascular and metabolic responses argues for these peripheral mechanisms having a variable contribution to the underlying pathogenesis of CFS. On the other hand, the more-uniform differences between the authors' CFS and control subjects in the targeted central serotoninergic and dopaminergic modulators may reflect a more global involvement of central neural mechanisms in the premature fatigue that characterises CFS.

Fear of movement in patients with Chronic Fatigue Syndrome Jo Nijs et al. Department of Human Physiology - Faculty of Physical Education and Physiotherapy - Vriie Umversiteit Brussel (VUB), Belgium.
AUTHORS' OBJECTIVE: This study was aimed at examining the prevalence of kinesiophobia (fear of movement) in patients with CFS. Kinesiophobia, a specific kind of fear-avoidance behaviour, is defined as "an excessive, irrational, and debilitating fear of physical movement and activity resulting from a feeling of vulnerability to painful injury or reinjury", and has been reported to be a common feature of Fibromyalgia and Chronic Low Back Pain patients.
AUTHORS' CONCLUSION: These data provide evidence for a high prevalence of kinesiophobia among patients with CFS. Future research should aim at examining clinical relevance of these observations in CFS, especially since Chronic Low Back Pain-related research has revealed that avoidance behaviour may be a consequence of long-lasting disability and that the process of chronicity is initiated by other factors.

Correlation of immunological parameters to psychological variables in Chronic Fatigue Syndrome Eike Van Hoof et al. Department of Human Physiology - Vrije Universiteit Brussel - Belgium.
AUTHORS' OBJECTIVE: Among the many patients who seek medical care for the complaint of fatigue, a small number suffer from the Chronic Fatigue Syndrome. Although numerous immunological abnormalities in patients suffering from CFS are described, these tend to be rather modest in nature with poor consistency between the different groups of patients studied. Moreover, among CFS patients the degree of immune activation seems associated with the severity of CFS-related physical symptoms, cognitive complaints, and perceived illness burden.
AUTHORS' CONCLUSION: Overall, the correlations reveal a strong link between psychological variables and immune parameters. The authors' results were already suggested by other authors. Indeed, this link could be mediated by cytokines. Increased levels of several cytokines are consistently found in this population. These cytokines could lead to both immunologic abnormalities and the patient's health dysfunction or at least the subjective belief of this physical dysfunction. This subjective belief of dysfunction was measured by the utilised psychological variables in this study and is better known as the acute phase response and is associated with sickness behaviour induced by cytokines. Instead of being pathogenic, this sickness behaviour helps the body to recuperate from various kinds of foreign agents. So, it might be that the psychological variables, instead of measuring well chosen psychologic/psychiatric constructs, only reveal sickness behaviour in this population.

Sertotonergic functioning in CFS and the harm avoidance subscale of the TPQ K. Busichio et al. Dept. of Neuroscience and Psychiatry, UMDNJ, NJ.
AUTHORS' OBJECTIVE: Understanding the neuropsychobiological correlates of CFS is crucial to finding a cure for this disorder. CFS has been associated with increased prolactin (PRL) responses to a variety of serotonergic receptor agonists and releasing agents, but contradictory reports exist. Christodoulou et al. 1999) found that CFS patients scored significantly higher on the Harm Avoidance Scale than healthy controls in the Tridimensional Personality Questionnaire (TPQ). High scores for the Harm Avoidance Scale have been found to be related to peak prolactin response to the 5-HTiA agonist flesinoxanin depressed and non-depressed patients (Hansenne et al. 1997,1999). The aim of the present investigation was to determine if subjects with CFS score higher on the Harm Avoidance Scale and show correlated increases in peak prolactin response to the rate limiting substrate in serotonin synthesis tryptophan.

AUTHORS' CONCLUSION: Many of the "serotonergic drugs" have effects attributable to activating other neurotransmitter systems. Tryptophan provides an increase specifically in serotonin and therefore, these data would indicate that this system is not perturbed in CFS. An alternative explanation is that increasing serotonin may result in compensatory changes in other systems, such as the dopaminergic system, which may counteract the effects of tryptophan on prolactin release. The authors did see the increased scores on the Harm Avoidance Scale as reported previously, but in CFS, this may not be driven by changes in the serotonergic system unlike the case reported for depressed and non-depressed patients. Future studies need to examine the dopaminergic system in order to confirm a normal relationship to prolactin release in CFS, since the effects of serotonin on prolactin release are mediated via a decreased inhibition of the dopaminergic system, and, in fact, it may be the disorders in this system that are characteristic of CFS. Supported by NIH grant # U01AI-32247.

The model of human occupation: a new approach to functional capacity assessment in CFS Renee R. Taylor and Gary W. Kielhofner. Department of Occupational Therapy, University of Illinois at Chicago, 60612, USA.
AUTHORS' OBJECTIVE: The authors introduced a widely used model of assessment in occupational therapy, the Model of Human Occupation described by Kielhofner, 2002. The Model of Human Occupation conceptualizes occupational participation as influenced by four factors, volition, habituation, performance capacity, and the environment. Empirically validated and reliable measures derived from this model were introduced, and a case study was presented to illustrate an occupational theory-driven approach to assessment for an individual with CFS.
AUTHORS' CONCLUSION: The Model of Human Occupation offers a comprehensive means of assessing occupational adaptation for individuals with CFS. The authors discussed how these results can inform future approaches to measuring functional capacity in this population.

Evaluating individualistic models of CFS Sharon Song and Leonard A. Jason. DePaul University, Chicago, IL
AUTHORS' OBJECTIVE: The Vercoulen et al. (J Psychosom Res 1998; 45(6): 507-17) structural equation model proposes that patients with Chronic Fatigue Syndrome experience severe fatigue because they attribute their symptoms to physical causes, are overly preoccupied by physical limitations, and do not maintain regular activity. This study assessed whether a model of CFS based purely on individual factors adequately describes this condition..
AUTHORS' CONCLUSION: The model seemed to better describe individuals who have psychiatrically explained chronic fatigue, and this study suggests that Chronic Fatigue Syndrome and psychiatrically explained chronic fatigue are not the same conditions.

Family medical history of persons with CFS Susan R. Torres-Harding and Leonard A. Jason. DePaul University, Chicago, IL.
AUTHORS' OBJECTIVE: The present investigation examined the occurrence of medical and psychiatric illness in the family history of persons with CFS, and then compared these results with the family history of medical illness reported by a control group of persons without fatigue. It was hypothesized that people with CFS would show a higher incidence of neurological, endocrinological, immunological, and autonomic system-related familial illness when compared to controls. It was also hypothesized that people with CFS would have a higher rate of familial fatigue/chronic fatigue and cancer when compared to the control group.
AUTHORS' CONCLUSION: Findings suggest an underlying familial predisposition toward the development of both CFS and autoimmune disorders. This finding is consistent with the hypothesis that CFS represents a dysregulation of the immune system.