Short summary of some of the findings presented at the Second World Congress on Chronic Fatigue Syndrome and Related Disorders, Brussels, 9-12 September 1999

These findings refute the incessant claim by Simon Wessely, now Professor of Epidemiological and Liaison Psychiatry at Guy's King's and St Thomas' School of Medicine, that ME / CFS is a "somatisation" (psychiatric) disorder.

This was the second international conference arranged by Professor Kenny de Meirleir and his team in Brussels, Belgium; medical experts from around the world, including some well-known and respected researchers, presented their most recent findings.

At the previous international congress held in Brussels in November 1995, Simon Wessely attended by invitation; at the 1999 congress, he was not an invited participant, so he chose not to attend.

Indeed, there was a veritable dearth of psychiatrists at the 1999 congress, a fact noted by Professor Daniel Peterson of the USA, who commented that at one conference, 99% of the presenters were psychiatrists, and that he was amazed at the misconceptions which existed about CFS.

Peterson said that ten years ago he believed CFS would be resolved by science; he had now changed his mind, and believed that it could only be resolved by politics.

Biochemistry of fatigue and pain

Dr Neil McGregor from the Department of Biological Sciences, Callaghan, New South Wales, Australia, spoke about The Biochemistry of Chronic Pain and Fatigue.

He presented data from four separate investigations of CFS using metabolite profiling techniques; several types of chronic pain and fatigue disorders were discerned.

Chronic pain was associated with reductions in serum sodium levels, changes in urinary volume, output of amino acids and other urinary metabolites, and increases in enzyme markers of tissue damage (ALT, AST). Increases in tyrosine / leucine ratios indicated changes in protein turnover, and were significant.

Fatigue was associated with alterations in the excretion of amino and organic acids associated with the tricarboxylic (citric) acid cycle.

Levels of RNase-L correlated with chronic fatigue and related symptoms.

Carriage of toxin-producing coagulase-negative stapylococci (which correlated with increased tyrosine / leucine ratios) was evident in 89% of CFS patients.

Changes in nitrogen homeostasis were associated with pain and fatigue symptoms.

Dr Henry L.Butt, a medical microbiologist from the University of Newcastle (Australia) research team discussed The Association of Stahylococcal Membrane - damaging Toxin and Chronic Fatigue / Pain, and reported that the increased prevalence of multiple carriage of coagulase - negative staphylococcus (which produces membrane-damaging toxins) was associated with increases in the tyrosine / leucine ratio, and that this indicated changes in the balance of proteolysis and protein synthesis, resulting in increased urinary excretion of the excitory amino acid glutamic acid, which correlated with musculo - skeletal symptoms, mood and cognition functions, and with an inverse association with temperature.

The toxin is hexameric and may function as an ion channel.

Overall, dysregulated proteolysis and increased excitory amino acids are events associated with chronic muscle pain.

In a separate lecture, Butt spoke about The Development of Laboratory-based Tests in Chronic Fatigue and Pain: Faecal Microbiology and Biochemistry. He reported that 60% of patients with chronic fatigue and pain have gastrointestinal problems, which supported the hypothesis of an altered gastrointestinal microbial flora.

These alterations in the microbial composition of the gastrointestinal tract may adversely affect the normal symbiotic processes.

There were also distinct differences in the faecal lipid composition in CFS patients, which showed significant correlation with gastrointestinal symptoms and in changes in the gut microflora.

Dr Hugh Dunstan, another member of the Newcastle, Australia research team spoke about The Development of Laboratory-based Tests in Chronic Pain and Fatigue: Essential Fatty Acids and Cholesterol.

He reported that EFAs are important for nerve functions, cell integrity, communications and membrane functions.

The mitochondria and myelin are affected.

CFS patients have significantly different fatty acid and sterol fasting plasma profiles from controls, and patients could be divided into different sub-groups on the basis of the profiles; in contrast, the control group was homogenous in their lipid profiles.

CFS patients have lower levels of cholesterol, which would adversely affect the membrane integrity and functioning, as well as steroid hormone synthesis, energy metabolism and bile production.

Viral infection can affect the nature of lipid-based anomalies in CFS patients.

Discriminant analysis showed clear differences between different CFS symptom indices.

This analysis provides a basis for treatment by lipid and micronutrient supplementation -- fish oils are less suitable (high arachidonic acid content) than vegetable oils. Division into biochemical sub-groups may provide a basis for individually-tailored management and treatment. His team recommends EFA supplementation, plus zinc, magnesium, manganese and vitamins A,C,E and B6.

In some CFS patients there is poor absorption as a result of a highly compromised gastrointestinal tract.

In a second paper, Dunstan spoke about The Development of Laboratory-based Tests in Chronic Pain and Fatigue: muscle catabolism and coagulase - negative stapylococci which produce membrane - damaging toxins.

In particular, he spoke about urine analysis, which is affected by the toxic chemical load, occult infections and altered homeostasis.

Their research data showed that CFS patients had reductions in total organic acid excretion.

Sub-groups of CFS patients could be delineated on the basis of their urine excretion and symptom presentation.

Muscle catabolism resulted in dramatic changes in urinary amino acids, particularly increases in tyrosine and 3-methylhistidine, with significant decreases in leucine, aspartate and phenylalanine. Pain severity was related to the tyrosine / leucine ratio and could be identified based on analysis of urine excretion and presented symptoms. Succinate levels were also reduced.

Membrane-damaging toxins (MDT -CoNS - coagulase negative staphylococci) were strongly correlated with catabolic responses and pain severity.

An unknown marker molecule (UM 27 –*urinary metabolite 27*), was elevated, and there was a positive correlation of pain with the levels of UM27, indicating that this may play a significant role in the aetiology and sustenance of chronic pain / fatigue disorder.

Dr H.Kuratsune from the Department of Haematology and Oncology, University Medical School and Department of Neuroscience, Osaka Bioscience Institute, Japan, spoke on Brain Regions Responsible for Fatigue Sense? --reduced acetylcarntitine uptake with PET into Brodmann's Area 9 + 24 in patients with CFS.

They found that most Japanese and Swedish CFS patients have a serum acetylcarnitine (ACC) deficiency and that this correlates with rating scores of fatigue.

They studied regional cerebral acetylcarnitine metabolism (rCMRac) and regional cerebral blood flow (rCBF) in CFS patients and in controls: there was deficient uptake in certain areas of the brain in CFS patients, particularly in Brodmann's areas 9 and 24, but also in the thalamus and other Brodmann areas 44,43,39,19,18, and in the anterior cingulate, the left temporal parietal cortices and basal ganglia, and this was correlated with rCBF.

Areas 9 and 24 are associated with cognitive, attentive and autonomic functions.

They concluded that biosynthesis of glutamate, aspartate and GABA in these areas may be impaired due to ACC deficiency, and this may explain the fatigue experienced by CFS patients.

Professor Tim Roberts from Australia presented details on Biochemical Abnormalities Associated with Visual Processing Disability (Scotopic Vision) in CFS.

Apart from fatigue, many other important problems are reported by CFS patients.

Disorders of visual processing in CFS patients include fatigue, lack of concentration (especially while reading),decreased visual span, abnormal pupil response, saccades and disturbed pursuit eye movements.

Similar anomalies have been identified in dyslexia.

Such problems are known as Scotopic Sensitivity / Irlen Syndrome (SSIS), and show an association with alterations in amino acid homeostasis, indicative of proteolysis, and changes in lipid metabolism.

He tried to ascertain whether biochemical anomalies in CFS may be related to these visual problems: preliminary investigation of urine excretion data show several metabolic abnormalities which may be associated with these symptoms and reported symptoms appear to correlate with the finding of protein catabolism, which suggests an underlying infective aetiology.

Immunology

Professor Nancy Klimas from the Clinical Immunology Laboratory, University of Miami School of Medicine, USA, gave a comprehensive and authoritative overview entitled Immunological Abnormalities in CFS.

She started by listing various factors affecting the immune system in CFS:

(i) genetic predisposition (51%)

(ii) triggering events (infections)

(iii) mediators (endocrinological and psychological factors)

and observed that the health outcome in any individual depends on how all these interact.

The role of the immune system in illness is twofold:

(i) it plays a direct role in contributing to the symptom complex: immune competence decides effective or defective prevention of reactivation of infections. When turned on, the lymphocyte antigen-driven response may generate a Type I response (CD4+, Th1, IL 2 / IL 12, INF - gamma, with activation of CD8+ cells that kill viruses). Lymphocytes play a vital role: they function through a messenger system -- cells have memories; they are antigen-driven and recognise infections, transplants, toxins, foods etc.

(ii) it plays an indirect role, because it interacts with the brain (it has receptors for neurotransmitters) and with the endocrine system (cortisol reduces inflammation through down-regulation of immune activation -- low cortisol in CFS could play a role in chronic immune activation. Stress has a profound impact on the immune system. Interaction with the hypothalamic / pituitary axis affects neurotransmitters and impacts on sleep. The Type II response (Th2, IL6, IL10, activation of B cells, and antibody production, (which prevents / clears infection) comes to dominate as the illness extends.

The importance of the 2-5RNase -L (a product of INF- gamma activation) leads to an up-regulation of RNA synthesis and pro-inflammatory cytokines, TNF -alpha and IL 1, which also disturb circadian rhythms.

Specific oligoclonal and not polyclonal antibodies are involved.

The effects of stress and negative life events were similar in CFS patients and in controls, but the long-term outcome depends on the shift from Th1 to Th2.

There is evidence of chronic immune activation: enzyme systems are up-regulated

(eg. interferon, 2-5A RNase L activation, mRNA (cytokines).

With regard to oligoclonal versus polyclonal activation, Klimas observed that there is a lack of abnormal serology to most latent viruses, suggesting that immune activation was antigen-specific.

There is evidence of cytokine abnormalities – cytokines change over time and with illness severity: TNF-alpha receptor expression increases with flares of the illness, and there is increased evidence of Type II expression as the illness persists for years.

Longterm, stress results in immune dysfunction illness (eg. reduced numbers
of

CD8 (supressor) cells, blunted growth hormone (GH) response and thyroid releasing factor (TRF), and increased corticotrophin releasing factor (CRF),

ACTH and cortisol, which Klimas pointed out was the *opposite* of what Demitrack claimed.[1]

Of interest is the fact that Klimas has found an *enlarged* adrenal mass, which is the opposite of Dinan's findings, where the right and left adrenals were found to be reduced in size by 50%.

Klimas said CFS was an excellent model of neuroendocrine-immune interaction and re-stated the PNI *(psychoneuroimmunological)* paradigm as a basis for understanding the complex relationships which underlie the extensive changes occurring in CFS patients.

She concluded by confirming that immune abnormalities play an integral role in the pathogenesis of CFS and that they contribute to the symptom complex, and that they interact with the autonomic and endocrine systems; the pattern and type of immune activation are equal to "cause and effect".

Professor Jonathan Brostoff from University College, London discussed Allergy in CFS.

He started by saying that it might be useful and practical to look at the 'total load' in CFS and try to alleviate the burden.

25% of ME / CFS patients are allergic, and this can be mistaken for CFS. In contrast, it was rare to see an allergic diabetic. Common culprits giving rise to food allergies are chocolate, grains, dairy products, coffee and citrus fruits, which can give rise to migraine, arthralgias, lethargy, myalgia, irritable bowel syndrome and vivid dreams. Hyperventilation is common and gives rise to breathlessness, pins and needles, scotopic vision, alkalosis and reduced blood magnesium.

Multiple chemical sensitivity was another add-on problem, where patients become extremely sensitive to drugs and inhaled chemicals.

All these provide add-ons to CFS and should not be mistaken for it.

If these add-on problems are treated (by an elimination diet, by micro-nutrient supplementation and by correcting breathing patterns), the total load would be less.

Brostoff believes that the IBS / opioid theory is not valid for more than 20% at most of ME / CFS patients.

He commented that almost 30% of the general population suffer from some form of food intolerance *(which is his area of speciality)*.

Dr L.Lambrecht , from the Department of Nuclear Medicine, University Hospital, Ghent, Belgium, spoke about The Chronic Fatigue Syndrome: Clinical, Immunological and Neuro-imaging Correlations in 500 patients.

He outlined results from an extensive battery of tests done on 500 consecutive CFS patients between January 1991 and May 1999. The tests included routine laboratory parameters and erythrocyte magnesium levels; lymphocyte phenotyping (CD8+ / CD38+ and associated T8 cell percentage); pulmonary function evaluation and maximal exercise tests; vital capacity and forced ventilatory capacity and inspiratory ventilatory capacity. Brain SPECT scans were performed (on 200 patients) and MRI scans were performed (on 30 patients). Polysomnographic results (on 250 patients) were related to SPECT scan findings.

SPECT scans revealed 294 lesions (mostly involving the left temporal lobe) in 148 patients.

MRI scans showed 17 lesions (demyelination foci) in 30 patients.

SPECT anomalies were more frequent and occurred in higher numbers compared with MRI scans.

Karnofsky scores (KS) were negatively correlated with significant neurospect anomalies, and also with CD+ / CD38+ cells, and with erythrocyte magnesium levels (which were reduced in 37% of cases).

A neurospect scan showed *no* perfusion in the brain stem of one patient, and an iodine tracer indicated glial cell inflammation.

Tiffeneau index and peak flow index were significantly decreased.

2% of patients showed a significant increase in airway resistance.

Lymphocyte phenotyping was significantly increased in 52% of cases and decreased in 0% of cases.

Splenomegaly was reported in 29% of cases.

Patients with CFS had significant psychomotor dysfunction (*eg. dizziness*, *vertigo*, *lack of balance, inability to judge and control distance and speed of own movements, inco-ordination)* and sleep disturbances.

All this supports the encephalomyelitic pathogenesis of CFS and illustrates the mutisystem involvement in CFS disability.

Dr Byron Hyde from The Nightingale Research Foundation, Ottawa, Canada spoke on Immune Abnormalities in 16 ME / CFS Patients.

This was a small study on 13 female and 3 male patients who were treated with isoprinosine.

These patients underwent extensive immune investigations.

Investigations showed that these subjects had significant and persistent abnormal immune changes in CD4, CD8 and NK cells, and in immune memory; key cytokines (IL-2) were increased, while IL-12 was almost zero. Others which were significantly decreased were IL-10 and IFN gamma. CD8 cells and NK cells were also decreased.

Each patient had one or more abnormal brain SPECT scan results which showed perfusion abnormalities ie. a vasculitis pattern, particularly in the left parietal frontal lobe in right-handed

people. This pattern is found in two thirds of autistic cases and resembles the HIV-encephalitic pattern found in one third of patients.

Epidemiology

Professor Paul Levine from George Washington University School of Public Health

outlined details on Chronic Fatigue Syndrome and Cancer: is there a relationship?

Immune dysfunction was an important aspect for one subtype of CFS and fatigue was arbitrary.

Grufferman's earlier study on cancer in a North Carolina symphony orchestra had persuaded them to research a cancer link in CFS more systematically.

Their aim was to see if CFS predisposes to cancer.

Details of the study were presented, and their results showed an increase in malignancies, notably brain tumours, non-Hodgkin's lymphoma, B-cell lymphoma, adenoid cystic carcinoma of the breast, transitional cell carcinoma of the bladder and uterine cancer. This pattern of cancers differs from the usual most common population cancers.

They tentatively concluded that a subgroup of CFS patients may be prone to develop cancer.

They propose to establish a register of those with CFS who develop cancer.

RNase-L in Chronic Fatigue Syndrome

Professor Bernard Lebleu from the Molecular Genetics Institute, Montpellier, France first presented The Interferon-Activavated 2-5A / RNase L Pathway: An Overview.

In this excellent overview, Lebleu explained that interferons are the most efficient agents in defending the body against pathogens, especially viruses, and are closely involved with the function of cell mechanisms. IFN-gamma (acting through membrane receptors) activates up to 20 different genes leading to a double stranded RNA which activates 2-5A synthetase.

It is associated with a variety of viral diseases.

2-5A is an unstable molecule with a half life of minutes. In successive transformation stages, this pathway becomes impacted in CFS. This also happens in other viral disease, eg. myocarditis and HIV viruses.

In CFS patents, this is degraded into a low molecular weight enzyme (RNase-L) which can exist in either an active or inactive form.

A natural inhibitor molecule (RLL) controls the balance between the active and inactive forms.

The active molecule degrades cellular RNA leading to inhibition of viral protein synthesis.

The 2-5A binding site requires a cystine-rich environment for RNA cleavage.

(Cysteine is the reduced form of cystine, which is a key amino acid important for maintaining the three-dimensional structure of all enzymes: in order for the substrate to react with the enzyme –ie. the RNA cleavage—it is necessary for the cystine-rich environment to be preserved, otherwise the three-dimensional enzymatic properties are lost. The disorder of the 2-5A antiviral pathway in CFS is in finding the low molecular weight enzyme.

The possibility of this disordered pathway being a response not only to viral presence but also to foreign chemicals such as organophosphate and fluoride ions (or to a deficiency of important mineral ions such as magnesium) is worthy of further investigation.

This has already been studied by Vojdani and Lapp [2] who set out to develop biomarkers for possible differentiation between viral-induced CFS -- . ie. those without sensitivity to chemicals – versus chemically-induced CFS. They concluded that 2-5A and PKR (protein kinase RNA) are not only biomarkers for viral induction of CFS, but biomarkers for other stressors in CFS, including certain chemicals).

There are now good techniques for identifying RNase-L in CFS patients.

In a second paper, Lebleau spoke of the *new* Low molecular weight RNase-L molecule (a 37KDA 2-5A binding protein) as a potential biochemical marker for CFS.

The identification of this new low molecular weight molecule was achieved in French / Belgian collaboration.

This particular binding polypeptide was found in 88% of CFS patients (in the peripheral blood mononuclear cells – PBMCs).

This 37 KDalton form of the enzyme was found only in CFS patients and not in controls, where the relative amount of 37KDA was very low.

Over-expression of this 37KDA protein leads to significant changes in cell and mitochondrial metabolism.

This appears to be another objective biochemical marker which accords with most of the many other markers presented at this Conference and may be a diagnostic marker for distinguishing CFS patients from healthy individuals.

Professor R.J.Suhadolnick from Temple University School of Medicine, Philadelphia, USA spoke about the Diagnosis of Chronic Fatigue Syndrome:

Determination of a Low Molecular Weight 37KD 2-5A-Dependent RNase-L in Peripheral Blood Mononuclear Cell Extracts.

This was a joint US / Belgian / French / German study.

Suhadolnick explained that in HIV infections, the 2-5A RNase-L pathway was shut down, but in CFS it was upregulated.

Two methods for determining the presence of RNase in peripheral blood mononuclear lymphocytes was described: the American group used a photochemically labelled azide probe, whilst the French group used a radiolabelled probe coupled with periodate oxidation of the ribose ring.

Both methods had a high degree of specificity and sensitivity: one method had 98% accuracy, the other was 100% accurate.

In both methods, statistically significant agreement with clinical diagnosis was demonstrated.

This represented a significant breakthrough: it took them deeply into the biochemical origin of CFS, indicating kinetic properties and possible regulation of this dysfunctional pathway, and it provided a possible diagnostic marker.

Although the methodologies are complex, they have been shown to be reproducible in different laboratories and to identify patients accurately.

Professor Kenny de Meirleir of the Free University, Brussels continued by outlining the Low Molecular RNase-L Pathway Abnormalities in Chronic Fatigue Syndrome: Its Use in Clinical Practice.

The presence of the LMW RNase-L 37KDA 2-5A binding protein appears to correlate well with the clinical diagnosis of CFS.

They therefore decided to study the abundance and presence of this LMW RNase- L in relationship to the following:

(i) the 1988 CDC criteria for CFS

(ii) bronchial hyper-reactivity

(iii) post-Ampligen treatment.

In test (I), they found that in 705 CFS patients, there was a clear correlation between the binding protein and the clinical symptomatology in patients who fulfilled both the 1988 *and* the 1994 CDC criteria for CFS

In test (ii), they found that in 162 patients with bronchial hyper-responsiveness to 2mg of histamine, patients were three times more likely to have a LMW RNase-L ratio greater than 1.

In test (iii) they found that a positive outcome after Ampligen treatment was inversely correlated with LMW RNase-L ratio in 24 out of 26 cases.

They concluded that a more pronounced RNase-L enzyme dysfunction correlates well with the original (1988) CDC definition of CFS (which related more to an acute*viral* onset).

Diagnosis

Dr Byron Hyde from The Nightingale Research Foundation, Ottawa, Canada spoke on The Technological Investigation of ME / CFS Patients, and stated that after 16 years, he still had problems in deciding what they are dealing with.

He gave a critical analysis of the failure of the CDC criteria, and of the CDC's failure to suggest types of investigations that would be helpful in elucidating ME / CFS.

Despite this, the following techniques have produced evidence to help the practising physician.

These include SPECT and PET scans, total blood cell and plasma volumes, and immune function studies.

SPECT scans have indicated deficiencies in cerebral blood flow, whilst brain pathology was found in cadavers.

In about 60% of patients, abnormally low RBC volumes were found: only proportions of red blood cells and plasma volumes are normal.

The 1992 CDC definition specifically stipulates glucose and TSH (thyroid stimulating hormone) tests – 40 -50% of patients develop thyroid problems.

A total cardiovascular work-up reveals that frequently there are CNS vascular occlusions.

Vasculitic patterns are identical to those in HIV patients.

There may be major valve pathology.

SPECT and PET scans show that huge areas of the brain are injured.

ME and CFS **are not the same**.

Determining disability in North America was very important – he often went to Court, and settlements are huge for this illness : between $0.5 million and $4 - 5 million, but physical changes must be demonstrated.

Professor Tim Roberts from the Newcastle, Australia research team spoke on The Development of Laboratory-Based Tests in Chronic Fatigue Syndrome: Investigation of Erythrocyte Oxidative Damage in CFS.

They investigated CFS patients by full blood counts, ESR, CRP haematinics, and markers for oxidative stress.

Their results showed that two markers of oxidative stress were identified in CFS patients: methaemoglobin (metHb) and malondialdehyde (MDA) markers were identified, and increased mean erythrocyte volume compared with controls, with significantly different blood parameter profiles.

Erythrocyte distribution width was the primary factor differentiating CFS patients from controls.

Statistical analysis showed that these parameters were associated with symptom expression and indices in CFS.

The MDA and metHb groups were associated with different symptoms and symptom indices.

In vitro studies demonstrated that RBCs reduced the interaction between activated neutrophils initiating chromium release from target cells by free radical mechanisms involving active oxygen species and nitric oxide.

Free radicals can cause much damage, to DNA and elsewhere.

Treatment to maintain the integrity of membranes, particularly RBCs, should be helpful in CFS / ME.

Dr G.Moorkens from the Department of Internal Medicine & Endocrinology, Antwerp, Belgium spoke about Characterization of Pituitary Function in 73 Patients with Chronic Fatigue Syndrome.

These researchers performed comprehensive hormonal testing, investigating growth hormone (GH), ACTH and cortisol responses to insulin-induced hypoglyaemia, argenine and clonidine stimulation. Nocturnal GH secretion and serum levels of IGF-1, free thyroxin and TSH were measured.

Their very detailed results showed that there were subtle but significant changes in the pattern of GH secretion in CFS patients, which need further study.

In particular, serum prolactin, TSH and visceral fat levels were all increased in these patients.

Such changes were observed only during insulin tolerance testing and nocturnal GH secretion.

Increases in visceral fat indicate GH deficiency.

They concluded that increased prolactin, TSH and abnormal GH secretion fit into the theory of dopamine deficiency and adrenal axis dysfunction.

Clinical Observations

Dr N.Posner from the Department of Social and Preventive Medicine, University of Queensland, Australia spoke about Patterns of Functional Impairment in CFS.

Using the SF 36 health status survey from 530 responders, the means for the eight dimensions were found to be markedly lower than in population norms.

The overall results indicated a marked pattern of impairment; it was similar to that found in the USA studies, but was dissimilar from other disease profiles, particularly depression.

There is a very significant functional impairment in this group of patients.

The researchers concluded that CFS / ME patients are severely disabled, needing home support.

Dr Katherine Rowe from The Royal Children's Hospital, Melbourne, Victoria, Australia discussed Does the Symptom Complex of Chronic Fatigue Syndrome Occur in Adolescents?

This was a very detailed, elegant and well demonstrated study involving 189 young people, in which it was shown that the symptom pattern and reported frequencies were consistent in all 189 subjects.

The reported symptoms were similar to those seen in adults, but prolonged fatigue after physical exercise, headaches, problems in concentration, sleep disturbances, abdominal pain and myalgia were particularly pronounced.

Careful conical assessment and extensive statistical analysis provided an excellent fit to the data for 24 symptom items by identifying one second order syndrome factor and five correlated first order factors (muscle pain and fatigue; neurocognitive; abdominal, head and chest pain; neurophysiological and immunological respectively).

The immunological symptoms had significant direct and indirect effects on the four other factors.

"In this sample, an alternative hypothesis of somatisation disorder could not be supported".

Dr G.C.Scroop from the Exercise Physiology Research Unit, University of Adelaide, Australia outlined Normal Exercise Capacity in Chronic Fatigue Syndrome

He described detailed results of an incremental exercise test on CFS patients and on sedentary controls.

They concluded that CFS patients are not deconditioned, and that graded exercise programmes are unwarranted.

Patients'Day

In the morning session, there was a debate on Name Change for Chronic Fatigue Syndrome, chaired by Vicki Walker of CFIDS Chronicle.

This clearly showed that everyone was dissatisfied with the term 'chronic fatigue syndrome', which was easily misunderstood: it stigmatised patients and focused on 'fatigue' only, when fatigue was not the most disabling problem.

There was no support for an eponym (ie. named after a person, eg Ramsay).

Both the Holmes 1988 and Fukuda 1994 definitions of CFS had muddied the waters.

Multiple sclerosis is well-defined, yet can have very differing characteristics.

"ME" still existed: there have been 60 epidemics this century.

"ME" offered greater legitimate recognition, and was accepted by the World Health Organisation. There was strong support for the term myalgic encephalomyelitis in the UK, Holland and New Zealand.

The US Congress would not consider the term myalgic *encaphalopathy*.

There was general consensus that this is a **brain dysfunction disease with a biochemical basis**: a new descriptive name should indicate the most significant aspects, ie. brain, muscle pain, lack of energy and a dysfunctional immune system (affecting the neuroendocrine system).

The afternoon session took the form of a CFS patients' meeting, when about 500 patients (mostly Belgian) filled the lecture hall. A summary of the Congress was given –much of it in Flemish—and some experts addressed the audience.

International lobby group

At this afternoon session, Simon Molesworth, a barrister from Australia and Chairman of the Australian National Trust (who is the father of a teenage boy with severe ME) made a passionate speech.

He said CFS /ME offered challenges in many forms --- first of all there is the question of *credibility*: having ME recognised as an illness presented more problems than with other illnesses. The physical nature was doubted by authorities, governments, pension agencies etc, and this doubt undermined essential support for those with ME / CFS.

Stories from around the world were the same – no government was comfortable with the concept of ME / CFS, and therefore patients were let down.

People fought battles with authorities all over the world.

There is an urgent need for stronger advocacy.

Politicians and governments *must* know that people with ME / CFS share the same view.

Molesworth announced that it had been decided that day to form an international lobby group as a voice for all concerned, and this idea had come from Professor Kenny de Meirleir.

A Charter would be drawn up to incorporate the following points:

1. Provide an international voice to represent ME / CFS people to national and international organisations

2. Ensure services are provided under Human Rights Laws

3. Secure support from governments, medical and social services

4. Sponsor sensible medical research and treatment for ME / CFS

5. Represent those in jeopardy

6. Ensure public education about ME / CFS as an illness; provide information and advocacy.

International groups (not merely the major patients groups and not individuals) would be members of this lobby group.

Professor Daniel Peterson from the USA said big changes were taking place and it was easier for the disability to be recognised.

Internationally we are all talking about the same thing and it is ridiculous to have different guidelines. All it needed was a one-line change in law: declare CFS / ME to be a**"medically determined disease"** *(which is already acknowledged by the World Health Organisation in the 10th International Classification of Diseases).*

With CFS, everyone was their own advocate, said Peterson.

Both Canadian and US representatives confirmed that CFIDS / CFS is now considered to lie somewhere between HIV / AIDS and Alzheimer's Disease.

The overall impression of Congress delegates is that there is a rapidly growing body of objective and physical measurements, which mean that (*quote*)"ME / CFS has now been taken out of the hands of the psychiatrists".

Particularly important and impressive is the evidence of the urinary metabolite profiles and plasma lipid profiles which, in extensive and objective statistical analysis, correlated with five different sub-groups of ME.

The infection - immune basis of ME has been strengthened.

Both SPECT and MRI scans clearly provide objective evidence of underlying central disorders in ME.

Many cross-links between earlier studies and the conference reports are now apparent.

The CDC definition of CFS is clearly not adequate.

It should be possible to sharpen the classification of ME into various sub-groups; this will help research, diagnosis and treatment.

Evidence presented on Gulf War Syndrome at the Brussels Congress

The Congress opened with the consideration of Gulf War Illness / Syndrome and with its relationship to ME and related disorders such as fibromyalgia syndrome.

Professor Ben Natelson from the DVA Medical Centre, East Orange, New Jersey

discussed findings in Gulf War veterans of inadequate cardiovascular support.

Professor Paul Levine, a Veterans' Association epidemiologist from George Washington School of Public Health, Washington DC confirmed that his study

"supports the possibility that environmental factors could be responsible for some of the complaints of Gulf War veterans".

Professor Garth Nicolson from the Institute of Molecular Medicine, Huntington Beach, California spoke on mycoplasma in GWS; his team have used cycles of antibiotics, but the response differs widely and there have been 600 reports of anaphylaxis in Marines after the Gulf War.

Professor Malcolm Hooper from the Department of Medicinal Chemistry at the University of Sunderland, UK, gave a most impressive and well-received lecture entitled "Towards a fuller understanding of Gulf War Illness / Syndrome" in which he explained that although lasting for a mere five weeks, the Gulf War conflict had been the most toxic war in military history.

UK soldiers were given 10 vaccines plus five or six undeclared (and unknown) injections, all records of which had been destroyed or were being kept by the MOD.

US soldiers had 17 vaccines by injection which included biological warfare agents (BWs), eg. anthrax, plague, botulin, Rickettsia, aflatoxins, plus NAPS (Nerve Agent Protection Sets) tablets (ie. pyridostigmine bromide -PBs); they were exposed to organophosphates (OPs),carbamates, organochlorines (OCs, eg. Lindane), pyrethroids, and DEET (an insect repellant as distinct from an insecticide).

The administered vaccines included several live vaccines, including typhoid, polio, Yellow Fever and measles.

The UK soldiers also received injections of Hepatitis A-Ig, *but this should never be used in conjunction with live viruses.*

When they were ordered to take the NAPS tablets, some troops experienced classic autonomic effects such as sweating and uncontrollable diarrhoea, which meant that their protection suits were soiled with their own excrement.

Deployed personnel were also exposed to chemical warfare agents such as mustard gas, and to the organophosphate analogues sarin, tabun and soman and Vx.

No informed consent was given by the soldiers.

Squalene was used as an adjuvant in experimental vaccines: HIV envelope genes have been found by Professor Nicolson in association with mycoplasma, indicating a possible gene modification of the mycoplasma, thereby enhancing their pathogenicity, which has a worrying potential.

Human endogenous retroviruses can re-arrange DNA – this can be detected in myeloma patients.

In addition there was toxic smoke from oil well fires, and there were problems with the troops' protection suits (quite apart from personal soiling).

The soldiers were exposed to solvents used in preparing vehicles; these and toxic fumes from oil fires are immunosuppressant and carconogenic, affecting the respiratory and gastrointestinal tracts.

There were also biohazards such as malaria, Leishmaniasis, fleas, scabies, lice and other insects, including sand flies and mosquitos.

A list published in JAMA in 1997 mentioned not only the biological warfare agents but also bacteria like brucella species, pseudomonas species and *Francisella tularensis.*

It was easy to design studies which give the desired result, said Hooper, but there was little doubt that the Gulf War veterans had received a cholinergic

"tripple whammy"; there was bound to be some synergism and it was to be expected that some esterases would be knocked out.

Hooper pointed out that almost the entire cholinergic system would be wiped out.

Could a person still function? he asked. The answer was No.

The central nervous system was affected, as were the autonomic and peripheral nervous systems --- under stress, substances and biological agents get transported across the blood brain barrier (BBB).

Of particular interest to Hooper was depleted uranium (DU), which is associated with Ranoactivity alpha, beta and gamma. DU shells have high penetration and are pyrophoric; when fired, they produce respirable uranium dust, which blows around. Some 300 tons of respirable uranium dust was created, which could travel up to 25 - 30 miles in a light breeze.

Some 1,200,000 rounds were fired from Tomahawk tanks and aircraft.

Helicopter pilots and VTOs were wearing casual clothes.

This dust persists: externally it can cause skin rashes; when respired, one third is excreted rapidly through the kidneys but two thirds accumulate in the throat, lungs and respiratory tract.

It gets into the bones, resulting in stem cell exposure, causing blood dyscrasias and cancer.

All the toxic substances to which the Gulf War veterans were exposed affect the central nervous system, and with the exception of DU, they also all affect the peripheral nervous system; some affect the autonomic nervous system and some affect the cardiovascular system and the blood.

Hooper discussed various diagnostic tests which ought to have been carried out on the Gulf War veterans; clinically these include neurological, immunological (IgA + cortisol), cardiovascular, renal and liver function tests, with tests for genetic markers.

RNA screening should be used to look for pesticide contamination and for evidence of depleted uranium.

SPECT scans should be used to look for brain perfusion levels.

Urine should be tested for levels of IAG (indolylacroylglycine); this test may show peaks of small peptides which indicate a “leaky gut”, which is associated with a compromised digestive system and with ensuing disruption of central nervous system and endocrine function.

Batteries of tests to asses oxidative status should be performed (eg GSH, selenium, zinc etc) and specific enzyme systems should be tested, eg. paroxonase activity, SOD, sulphur transferase and esterases; membrane stability should be assessed.

Levels of nutrients and micro-nutrients should be assessed and monitored, including a Niacin flush test (for vitamin B3); gut function and permeability should be assessed, as should pancreatic function.

Endocrine responses should be assessed.

NB. On his own admission, in his official study of Gulf War veterans Wessely performed no clinical examination or laboratory investigations. He worked only from a self-report questionnaire which was sent only to selected veterans, yet he confidently concluded that there is no such thing as Gulf War Syndrome and the MOD accepts his study.

Hooper said that a pattern is emerging: there is a primary insult, which may be neurological. Vaccines are primarily immunological insults, thus the immune and endocrine systems are affected, which in turn affect the gut and brain tissue.

The blood brain barrier is crossed, and an entire cascade of processes ensues, affecting the central nervous system, the pineal complex, opioids, the endocrine system (gonads, thyroid and adrenals); through the olfactory system the limbic system is affected, which in turn affects the central nervous system: there is a direct link between the immune system and the CNS.

Despite Wessely's view that there is no evidence of birth defects in Gulf War veterans, reports from America indicate that in one state alone (Mississippi), 67% of children born to Gulf War veterans have birth defects.

Hooper provided statistics showing that 9,000 Gulf War veterans were now dead

(and these were previously fit and healthy young men); there are 230,000 medical cases, of which 203,000 have filed claims.

From the UK alone, 53,000 troops were involved in the Gulf War, but we do not know how many are ill or how many are dead, because the only epidemiological study on UK veterans is the one done by Wessely.

Hooper strongly challenged the official UK stance.

He also pointed out that syndromes which overlap with Gulf War Syndrome include ME.

This Appendix has been compiled in collaboration with Professor Malcolm Hooper and Doris M.Jones MSc, to both of whom grateful acknowledgment is made.

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[1] Evidence for Impaired Activation of the Hypothalamic-Pituitary-Adrenal Axis in Patients with Chronic Fatigue Syndrome. Mark A.Demitrack et al.*Journal of Clinical Endocrinology and Metabolism. 1991:73:6:1224-1234*

[2] Interferon-induced proteins are elevated in blood samples of patients with chemically or virally induced chronic fatigue syndrome. Vojdani A, Lapp C. *Immunopharmacol Immunotoxicol 1999:21:2:175-202*