ME/CFS (Myalgic Encephalomyelitis/Chronic Fatigue Syndrome) in Australia

"The release of the Canadian Consensus Clinical Guidelines Overview has provided Australian sufferers and their medical advisors with a new baseline for definition, diagnosis and treatment of ME/CFS. These guidelines have been unanimously endorsed by the Australian ME/CFS Societies as representing the current world best practice for Clinical Guidelines. The Australian Societies wish to see these guidelines used by Australian GP's to diagnose and manage this illness."

- Simon Molesworth AM, QC, Chairman, ME/CFS Association of Australia Ltd

Some 140,000 ME/CFS Australian sufferers (more prevalent than AIDS or Lung Cancer[1]). Annual cost to the Australian economy of around $3.8 billion[2]

Overview of ME/CFS

- Myalgic Encephalomyelitis (ICD 10 G93.3), which includes CFS, is classified as a **neurological disease** in the World Health Organization's International Classification of Diseases (ICD) and is described as a 'not uncommon medical disorder that causes significant ill health and disability in sufferers' [3] (N.B. "Myalgic Encephalomyelitis" and "Chronic Fatigue Syndrome" have become interchangeable so this illness is commonly referred to as "ME/CFS" [4])
- ME/CFS is a broad diagnosis that includes a spectrum of clinical syndromes of neuro-immune diseases linked to known infectious agents including Ross River virus, Epstein Barr virus, Q fever, Lyme disease, and toxic exposures such as organophosphates. These syndromes are characterized by neurological, gastrointestinal, cardiovascular and myoarthralgic features. Severe forms can present with paresis, seizures, intractable savage headache, and life threatening complications. The renaming to chronic fatigue syndrome in 1988, giving misplaced emphasis to "fatigue", trivialises the substantial disability of ME/CFS which can extend to the wheelchair or bed-bound, requiring 24 hour care.
- Given the cost of ME/CFS to the community there is a distinct lack of relevant research funding in Australia directed towards biomedical research into the causes and treatment of post-infective and other forms of ME/CFS. Government grants for ME/CFS research are largely diverted towards unrelated 'fatigue' oriented or psychiatric investigations. Consequently ME/CFS Societies and related groups rely heavily on overseas research for information.

  At the 2004 US Centre for Disease Control (CDC) sponsored conference of the American Association for CFS (AACFS) William Reeves, Chief of the CDC CFS Research Program reported:[5]
  - ❖ US $9.1 billion (WalMart Gross Profit) of earnings lost annually due to CFS
  - ❖ CFS patients are sicker with greater consequent disability than patients with chronic obstructive lung disease or cardiac disease
  - ❖ the strongest predictor of the development of post-infectious (chronic) fatigue syndrome is the severity of the acute illness at onset. (Psychological factors played no role in the development of CFS following infection)
  - ❖ fewer than 16% of CFS sufferers in the general population are diagnosed
- It's known that prior to onset of ME/CFS, sufferers were well and leading active lives. Their onset of ME/CFS resulted from some event, such as a viral illness. Many recover (with

[1] Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Clinical Case Definition and Guidelines for Medical Practitioners: An Overview of the Canadian Consensus Document by Bruce M. Carruthers & Marjorie I. Van de Sande
[2] Figures based on information from the US Centre for Disease Control (CDC)
[3] ME/CFS Guidelines - Management Guidelines for General Practitioners, South Australian Department of Human Services
[4] An Overview of the Canadian Consensus Document ibid
[5] American Association for Chronic Fatigue Syndrome (AACFS) Press Release October 7, 2004

diminished capability) to rejoin the main community and take up their schoolwork, join the workforce, etc.

- The many symptoms presented by ME/CFS sufferers complicate diagnosis and treatment by most GP's. These symptoms range from muscle aches & pains; neuro-cognitive dysfunction (e.g. poor concentration & memory); gastro-intestinal symptoms (e.g. irritable bowel); orthostatic intolerance (e.g. low blood pressure); etc.
- People with ME/CFS can be affected for 2 – 10 years, though it is known that a number remain debilitated for longer periods, such as 20 years, and require full time care. Death can result from these severe cases
- The UK Parliamentary Gibson Report[6] accepted the bio-medical basis of ME/CFS; affirmed the WHO definition and key criteria of the Canadian Guidelines; identified vested interest in the benefits and insurance industry with regard to support for ME/CFS patients and their carers; called for new investment into research; and, provided a parliamentary agenda for change that is realistic and has won the support of many ME/CFS groups in the UK
- "after 3000 research studies there is now abundant evidence that ME/CFS is a real physiological illness" US CDC, 2006:

Significant Issues facing ME/CFS communities:

- Lack of understanding of the illness by the Medical profession and division within the medical community on treatment and management of ME/CFS.

  This lack of understanding sets ME/CFS apart from other chronic illnesses, such as MS, Asthma, diabetes, etc. Which in turn complicates management of the illness and the ability to develop prevention strategies within the community.

  The Canadian ME/CFS Consensus Clinical Guidelines provide a way forward to address this lack of understanding and management of the illness.

- Difficulties of correct diagnosis of the illness.

  Using the CDC figures above, some 84% (5 of 6) sufferers are mis-diagnosed. Such mis-diagnosis can result in inappropriate medical management of the illness that can exacerbate the severity of the condition.

- Lack of official recognition by the Department of Health and Aging that ME/CFS is a 'disability'
- Lack of support for groups dedicated to assisting those with ME/CFS
- Current Australian research is based largely on academic or evidence based data. It does not take account of "best practice" primary research carried out overseas or within Australia

What do the ME/CFS Societies want to see during 2007/08?

- Improved Australian diagnosis and management of ME/CFS through the use of the Canadian ME/CFS Consensus Clinical Guidelines
- Provision of funds and access to expert resources to improve support services to ME/CFS sufferers and their carers, to fund research into ME/CFS, and to raise awareness within the community on management and prevention strategies
- Provision of funds for core funding for a Research and Reference Centre to study all aspects of Q fever and rickettsial infections and associated post infection chronic fatigue syndromes by Professor Barrie Marmion AO, Q Fever Research Group & Professor Stephen Graves Australian Rickettsial Laboratory, Hunter Area Pathology Service University of Newcastle.

[6] UK Parliamentary Inquiry into the status of CFS/ME and research into causes and treatment. November 2006. Group on Scientific Research into Myalgic Encephalomyelitis (ME). Dr Ian Gibson MP (Chair)

Current status of ME/CFS research

Summary

For years ME/CFS research has yielded inconclusive results because the definitions used to select patients have been vague and over-inclusive[7]. [These include Fukuda CFS Research Criteria (CDC 1994), Oxford (1991) and London (1993)] There is hope that better targeted research can yield significant results.

Internationally too little effort has been spent investigating the biological basis of the disease. Instead, money has poured into programs exploring cognitive therapies and exercise programs. At best these provide symptomatic relief. They do not deal with the cause of the disease.

The chronic illness of ME/CFS often follows an acute episode that had hallmarks of a bacterial or viral infection. But for technical laboratory reasons the infecting agent was often not identified conclusively. In very early studies, 30 or more years ago, an association of ME/CFS with glandular fever (EB Virus) was recognised. However not all cases of CFS have evidence of EB virus Infection and only a small number of +EB virus infected patients develop ME/CFS.

Because of these early ambiguities the condition has been the target of derision and a fertile field for alternative medicine. Intensive efforts have also been made to explain it in terms of psychiatric dysfunction that have not yielded a coherent view of its pathogenesis.

There is a significant body of research into ME/CFS that have found Biomedical Abnormalities[8] in:

- Immune System, including
  - Chronic immune activation and dysfunction – evidence of persistent viral infection; activation of the 2-5A anti-viral pathway; low natural killer cells and cytotoxicity; T-cell abnormalities; pro-inflammatory cytokines and inflammation; increased cell apoptosis (death) and allergy
  - Abnormal immuno-genetic expression
- Brain/Central Nervous System, including
  - Objective measurement of dysfunction – deficits in working memory, concentration, information processing, autonomic function (including neurally mediated hypotension and orthostatic intolerance)
  - Abnormalities – regional brain hypoperfusion by SPECT, white and gray matter abnormalities by MRI, inflammation, hypomyelination, neurotransmitter and metabolic dysfunction by MRS/PET and abnormal spinal fluid proteins
  - Abnormal neuro-genetic expression
- Endocrine System: impaired activation of the hypothalamus-pituitary-adrenal (HPA) axis and abnormalities of neuroendocrine-genetic expression
- Heart and Circulatory System: hypoperfusion, impaired vascular control (including abnormal response to acetylcholine), low blood volume, vasculitis (including raised oxidative stress, inflammation and arterial stiffness) and heart dysfunction
- Muscular: structural and biochemical abnormalities including impaired muscle recovery after exercise (exercise responsive gene expression abnormal, worsening after exercise)
- Others: gastrointestinal dysfunction including food intolerance and IBS, mitochondrial dysfunction including abnormal mitochondrial associated gene expression and ion transport channelopathy

[7] Jason, LA et al. (2000). *Defining chronic fatigue syndrome: methodological challenges.* Journal Chronic Fatigue Syndrome Vol 7(3): 17-32.

[8] *There are some 166 references from Clinical and Research literature that detail these Biomedical Abnormalities. These can be provided upon request*

Adelaide Research

An ME/CFS data base for future ME/CFS research projects has been developed through the collaborative efforts of Dr Richard Burnet, Department of Endocrinology and Metabolism, Royal Adelaide Hospital, Dr Peter Del Fante Adelaide Western GP Network, and Professor Justin Beilby and Kristen Clarke Department of General Practice University of Adelaide.

Dr Richard Burnet, Department of Endocrinology, Royal Adelaide Hospital has concentrated on biomedical research into ME/CFS - electrolyte response to exercise, total body potassium measures, and gastric emptying studies.

A major research project involving the Department of Endocrinology Royal Adelaide Hospital, and the Department of Nuclear Medicine, Queen Elizabeth Hospital commenced early in 2007.

An Emerging Paradigm for ME/CFS[9]

Taken from material presented to the ME/CFS Research Forum Report Adelaide Research Network 3 - 4 June 2005. Presentations summarized the large amount of existing ME/CFS research that showed measurable physical abnormalities, and contrasted the dearth of adequate science in psychiatric claims.

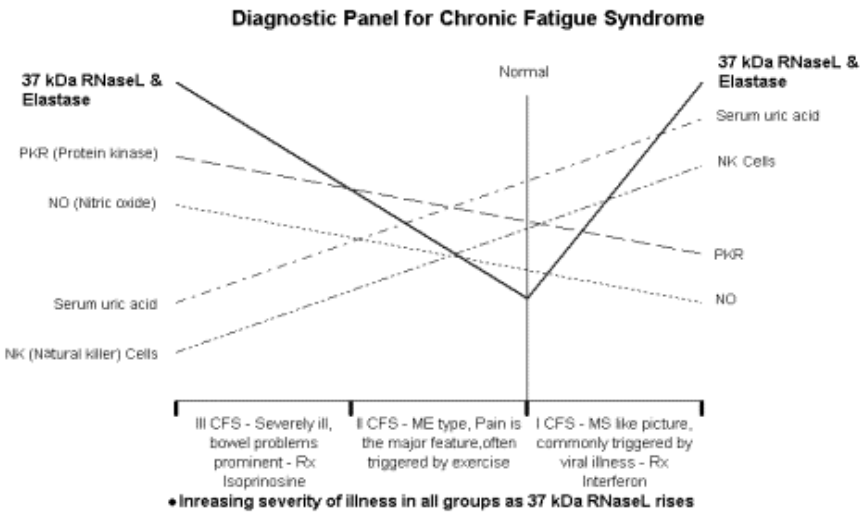
The keynote speaker was Professor Kenny De Meirleir, Professor of Medicine at the Free University, Brussels, Belgium. His clinic sees 800 CFS patients every three months, coming from many parts of Europe. He has 50 papers awaiting publication about this condition, many dealing with molecular biology as it impinges on aetiology, treatment and prognosis. Professor De Meirleir presented an epitome of over 5000 research papers on the topic since 1999.

In brief, a substantial sector of ME/CFS is due to 8-10 different genera of small bacteria that have in common a requirement to replicate in or on living tissue cells and to persist for long periods or indefinitely in the infected person.

In a minority of patients with a particular immunogenetic background loss of control of the level of persistent infection leads to immune stimulation that in turn produces the ME/CFS/PIFS symptoms. Ultimately further loss of control may lead to other chronic complications such as endocarditis. Similar considerations apply to certain persistent virus infections also acting against predisposing immune gene backgrounds (but without endocarditis as an endpoint).

On the basis of six tests performed by Belgium researchers, ME/CFS patients tend to fall into three broad groups, sometimes with overlap. These have differing aetiologies, treatment and severities. These are seen in Figure 1, which obviously does not show definite test values, but overall trends. For example, a normal patient has no LMW RNaseL. However the severity of all groups increases as LMW RNase L increases. Levels over 5 units are quite ill. Some patients, moribund with levels of 500 units are still being told their problem is in their heads.

Figure 1.



[9] Dr Michael Barratt MBBS FRCPA**.** *Current Perspectives* ME/CFS Research Forum Report Adelaide Research Network 3 - 4 June 2005 University of Adelaide

GROUP 1: *These have high LMW RNaseL levels, high uric acid, low Protein Kinase, reasonable NK killer cell levels, and low or normal NO*.

This group, about 15-20% of CFS sufferers, tends to have a multiple sclerosis type picture. Pain is not a strong feature. They tend to be associated with one or more of a long list of well known suspects, micro-organisms such as, brucellosis, Q fever, cytomegalovirus, glandular fever, Herpes virus 6A, Epstein Barr virus, enteroviruses, Lyme disease, mycobacteria, Leishmaniasis, mycoplasma; and pesticides, and heavy metals, to name but a few members of a vast rogues gallery. A staggering 20% of this group has low grade Herpes virus 6A encephalitis, a little known fact! Treatment is aimed at removing causes, if possible, with antibiotics, and anti-viral therapy, often with the addition of Interferon therapy.

GROUP 2: *LMW RNaseL up, PK up or not, Uric acid and NK down a little, NO is up. This group, about 60% of CFS patients, has pain as a predominant feature.*

Pain is often generalized and does not follow nerve root distribution. It may be aching, burning, sharp or shooting. Many patients develop many types of new onset headaches, including migraines, tension and pressure headaches. There is often generalized myalgia, and arthralgia. There is an overall reduction in pain threshold, (allodynia). The pain is often triggered by exercise.

This group is referred to as the ME (myalgic encephalopathy) group, in contrast with the Group 1, MS type.

GROUP 3: *this severely ill group, about 15% of patients, have very high LMW RNaseL levels, (up to 500 or more), high Protein Kinase activity, very low serum Uric acid, and severely depleted Natural Killer Cell activity.*

They usually have severe bowel problems, such as total bowel paresis, or retrograde faecal vomiting. There is a high mortality in this group, sometimes due to suicide. Many of these patients are living in survival mode, and are often abandoned by the medical profession as being in the “too hard basket”.

The gut is an important part of the immune system. We must get past the notion that it is only a conveyor belt for nutrients, or some sort of septic tank. If spread out, its surface absorptive area is about the area of the Sydney Cricket Ground! All patients at Professor De Meirleir’s clinic have serum Ig M and Ig A tests against a panel of 12 gut pathogenic bacteria. Any patients with a positive Ig M for any of these are given a cycle of one weeks antibiotics, followed by three weeks probiotics. 58% of patients have improved after three months, and interestingly, the serum Elastase drops.

Group 3 patients also seem to be helped by Isoprinosine, an immuno-stimulator drug which has proved helpful in delaying the onset of AIDS in HIV positive patients.

There is an encouraging support for the validity of these three CFS groupings. Professor De Meirleir took a large number of new CFS patients referred to his clinic and performed all the above six tests before the patients were seen clinically. On the basis of the test results he penciled onto their files his predictions as to their clinical symptoms. He was correct in 95% of the cases! The other 5% had overlap features.”