# Facts from Florida

**Margaret Williams** **16th February 2007**

The 8th International Association of Chronic Fatigue Syndrome (IACFS) Conference was held at Fort Lauderdale, Florida, from 10th-14th January 2007. This synopsis is not intended to be a detailed report of the Conference; it simply lists some key points that people may wish to use in their dealings with uninformed healthcare professionals. It is taken from the published reports of conference attendees (including Dr Charles Lapp, Dr David Bell, Dr Rosamund Vallings, Dr Lesley Ann Fein, Virginia Teague, Pat Fero, Cort Johnson, John Herd and Pamela Young, whose various reports are on the internet (mostly on Co-Cure), to whom grateful acknowledgment is made.

- The conference was attended by over 250 clinicians and researchers from 28 different countries and there was a strong sense that they were all co-operating to build on the science. It is the science that has freed the world from any doubt that ME/CFS is a legitimate disease with an aetiology that is not rooted in the psyche -- Japanese and Swedish research teams collaborated in a comprehensive study of a neuro-molecular mechanism and concluded that ME/CFS is an organic disorder. It was described as "this miserable illness".

- The latest figures (January 2007) on the economic impact of ME/CFS in the US are between $22 billion and $28.6 billion annually; in Japan, the figure is over $10 billion annually. The Japanese Government recognises ME/CFS as a real threat not only medically but also economically and has initiated a large research programme into causation and treatment.

- One of the most striking elements was the convergence of research findings: the three areas that came up again and again were inflammation, mitochondrial abnormalities, and vascular problems.

- Three separate research teams found evidence of microvascular problems in ME/CFS.

- The significant confluence of findings on elastase (a protease enzyme, i.e. it digests and degrades a number of proteins, including elastin, a substance that supports the structural framework of the lungs and other organs); vascular problems; apoptosis (programmed cell death); free radical production (highly damaging to DNA, to cell membranes and to proteins); and inflammation was undeniable.

- Research findings addressed many areas and provided yet more evidence that cognitive processing differs in ME/CFS compared with controls; there is evidence of distinctive chemical and molecular differences in ME/CFS patients; there is evidence of the role of specific viral agents, and there is confirmation that differences in gene expression exist between ME/CFS patients and healthy controls, as well as between subgroups of "CFS".

- The importance of sub-typing was recognised and emphasised.

- Dr Ellie Stein from Alberta, Canada, pointed out that suicide is the third leading cause of death in ME/CFS (the others being cancer and heart disease).

- In ME/CFS, testing for elastase, RNase-L, C-reactive protein, selected cytokines and NK cell activity are recommended because they are objective markers of pathophysiology and severity. In addition, an exercise test/re-test of cardiopulmonary function is necessary because it is 100% objective and confirms reduced functional capacity as well as post-exertional malaise for disability purposes. Further, lipid abnormalities and evidence of metabolic syndrome should be looked for.

**Cardiovascular system**

- Researchers are developing methods to measure cardiovascular and cardiopulmonary health in ME/CFS patients, which relates to oxygen consumption.

- ME/CFS patients' ability to work is impaired, as shown by an abnormal exercise stress test. Margaret Ciccolella and Christopher Snell et al from Stockton, CA, demonstrated that patients show extreme abnormalities in a next-day/second session of exercise. They do not recover in 24 hours. In one study, only one patient had recovered to baseline within 48 hours. These changes in serial testing point to a significant and confirmable physical abnormality, verifying the cardinal symptom of post-exertional malaise. This test/retest exercise test is 100% objective and can prove to the disability companies that ME/CFS is neither malingering nor faking. In ME/CFS patients, the measurements declined by about 25%, far more than in other significant diseases such as COPD and even heart failure.

- Post-exertional malaise following exercise challenge results in fatigue, light-headedness, vertigo, joint pain, muscle pain, cognitive dysfunction, headache, nausea, trembling, instability, and sore glands.

- In ME/CFS patients, there is cellular hypoxia — oxygen is delivered to the cells of the heart, brain, skeletal muscle and other organs, but the process of turning oxygen into energy is derailed.

- Graded exercise therapy is ill-advised — if a patient has abnormal oxygen consumption, muscles will not have enough oxygen and exercise will result in relapse.

- A US NIH-funded trial by Barry Hurwitz, a colleague of Professor Nancy Klimas at the University of Miami, found that 70% of ME/CFS patients have a low red blood cell volume. Treatment to increase blood volume was ineffective in respect of exercise tolerance and fatigue.

- One of the highlights of the conference was the presentation of Dr Vance Spence's work (University of Dundee) on inflammation and arterial stiffness in patients with ME/CFS – arterial stiffness is rarely found in adolescents, but in ME/CFS these young patients had higher levels of arterial stiffness than diabetic patients. This work looked at inflammatory factors (free radical by-products and C-reactive protein, an inflammatory marker) and found abnormally high levels of free radical by-products and C-reactive protein in patients but not in controls. C-reactive protein levels were significantly correlated with increased arterial stiffness. A likely cause is elastase. Elastase is a central factor in Professor Kenny de Meirleir's RNase-L paradigm (see below), and Dr Baraniuk's cerebrospinal fluid proteome study suggests elastase is implicated in blood vessel problems in the brain of ME/CFS patients. The logical consequences of increased arterial stiffness are exercise intolerance and diastolic (cardiac) dysfunction. The circulatory problems seen in ME/CFS may originate in endothelial cells lining all blood vessels. These cells are involved not only in opening and closing blood vessels but in the immune response as well, and they are often attacked by pathogens.

- Dr Paul Cheney (Mayo Clinic) found evidence of diastolic (cardiac) dysfunction in ME/CFS, with evidence of another cardiac abnormality (patent foramen ovale, or PFO). This results in hypoxia (low oxygen levels relative to metabolic needs).

- Cheney stated that the cardiac index of ME/CFS patients is so severe that it falls between the value of patients with myocardial infarction (heart attack) and those in shock.

- Mark van Ness from the University of the Pacific found that maximum aerobic capacity ($VO_2$ peak) is reduced in ME/CFS compared with sedentary controls.

- Van Ness found that oxygen capacity at the anaerobic threshold is reduced in ME/CFS.

- Van Ness also found that serum lactate is elevated, suggesting an abnormally early shift to anaerobic metabolism.

- In a subset of patients, Martin Lerner (Wayne State University, Detroit) described persistent EBV and/or CMV in ME/CFS patients: in addition to having high titres, all 37 patients studied had an elevated heart rate at rest, recurrent T-wave inversion on Holter monitoring, cardiac abnormalities and/or biopsy-proven cardiomyopathy. Symptoms included not only tachycardia but chest pain and syncope.

- According to Lerner, all ME/CFS patients have abnormal T waves; inversion is seen in 96%; there is resting tachycardia. Cardiac biopsies show fibrosis, myofibre disarray and fatty infiltrates.

**Nuclear Medicine**

- New methods in viral studies using refined technology show further abnormalities in subsets of ME/CFS patients. Increased use of instruments like MRI, SPECT/SPET, PET and fMRI show some of the abnormalities in functioning that patients with ME/CFS experience on a daily basis but these may not have practical application if a patient cannot have this testing done. A number of abnormalities with reduced responsiveness on fMRI is an essential feature of ME/CFS.

- Brain imaging shows that, amongst other abnormalities, ME/CFS patients have reduced blood flow to the brain (especially to areas that are involved in autonomic nervous system functioning and in sleep, concentration and pain, including the pre-frontal cortices, the anterior cingulate and the cerebellum); altered patterns of brain activation; reduced grey matter volume; altered serontonergic neurotransmission and reduced acetyl-carnitine uptake.

- A collaboration of researchers from Spain, Belgium and Australia used SPET scanning to observe patterns of brain activity; they found that the brain abnormalities correlated with abnormal immune results.

- Patients with ME/CFS require more brain regions to perform tasks, ie. they have to work harder to achieve the same results as healthy controls.

- One particular area of the brain – the Wernicke area, essential for understanding and formulating coherent speech—showed evidence of reduced activity after exercise.

- Proton resonance spectroscopy showed greatly increased levels of brain metabolites (lactate levels were 300% higher than in controls).

- According to Dr Tae Park from South Korea, the unexplained bright spots on MRI scans of some ME/CFS patients are evidence of an “arteriolar vasculopathy” or a blood vessel disease. He believes ME/CFS is a “systemic micro-vascular

inflammatory process" – a process that would affect not only the brain or the heart or the muscles, but potentially every organ system in the body. Dr Park found not only capillary inflammation and perivascular cuffing (the accumulation of immune cells that surround injured blood vessels), but that all the ME/CFS patients in his study demonstrated remarkably reduced renal blood flow. Dr Park noted that diabetics with renal vascular disease also complain of profound fatigue.

- Dr Hiro Kuratsune from Japan gave a summary of what is known about brain function in ME/CFS. It has been known for over a decade that frontal and temporal lobe blood flow is reduced in ME/CFS, and that exercise exacerbates this reduced blood flow for up to 72 hours. The new evidence is that elevated elastase and RNase-L levels correlate with reduced blood flow. It is known that the MRI is abnormal in the majority of people with ME/CFS due to numerous T2 weighted hypertintense foci, with evidence of demyelination.

- Patients with more brain abnormalities tend to be more physically impaired.

- The remarkable similarity in the brain images of patients with ME/CFS and multiple sclerosis was noted.

- Dr Gudrun Lange from New Jersey, USA, stated what can be said with certainty about the central nervous system findings in ME/CFS:

    1. the major cognitive problem seen is in information processing
    2. studies showing reduced cerebral blood flow are starting to show consistency
    3. there is a problem with serotonergic neurotransmission in the hippocampus and anterior cingulate regions
    4. there are spinal fluid abnormalities
    5. fMRI studies are showing altered patterns of brain activation.

**Proteomics**

- Proteomics is the study of proteins made in the cell, particularly their structure and function. Investigations into proteomics in ME/CFS are surging forward in many countries.

- Proteins predictive of ME/CFS were found in patients that were absent in healthy controls.

- Dr James Baraniuk from Georgetown University, Washington DC described the (quote) "unbelievable" finding of unique markers in the cerebrospinal fluid of ME/CFS patients that are completely absent from the control group.

- The proteomic biosignature of ME/CFS in the cerebrospinal fluid shows:

    1. a protease/antiprotease imbalance is present: alpha 2 macroglobulin (anti-protease) and orosomucoid 2 (anti-protease); this implicates increased elastase production
    2. several proteins suggest that amyloid deposition in the blood vessels of the brain is causing micro-haemorrhaging (amyloidosis is the deposition in the tissues of a starchy, waxy protein substance; the organs most affected are the liver, kidneys, spleen and heart; it occurs in conditions of chronic inflammation)
    3. one protein present suggests altered (increased) rates of apoptosis (ie. programmed cell death, a well-documented finding in ME/CFS)
    4. another protein present suggests free radical production is occurring
    5. another protein suggests problems with vasoconstriction and endothelial damage (pigment epithelial derived factor and endothelial proliferation associated with vascular dysregulation)
    6. another protein is associated with inflammation.

- One protein that was found – keratin – is of particular interest: it is associated with inflammation of the leptomeningeal cells in the membranes covering the brain and spinal cord.

- This proteome is not found in healthy controls.

**Virology**

- Of special interest was the study from Stanford University School of Medicine by Dr Jose Montoya: this was a groundbreaking study on anti-viral therapy for patients with elevated antibodies to HHV-6 and EBV; with a $1.3 million grant, this study will shortly be repeated among a subset of patients who have viral-induced dysfunction of the central nervous system.

- Japanese researchers looked at the reactivation of HHV-6 and HHV-7 in ME/CFS. These viruses have life-long latency. It is vital to distinguish between chronic, active and latent infection.

- Dr Dharam Ablashi from Santa Barbara, USA, showed that RNase-L was found to correlate with HHV-6 infection in ME/CFS and that RNase-L protein is a marker for active infection.

- Some patients clearly have a persistence of virus in their brain.

- Enterovirus infections have previously been reported in UK studies but have not been much explored by US researchers. Enteroviruses are a genus of RNA viruses that includes echovirus, coxsackie virus and poliovirus. In a recent US study by John Chia from California of 108 patients with ME/CFS who underwent gastric biopsies, 100 revealed chronic inflammation and 80% were positive for VP1 (enteroviral capsid protein – first used by Professor James Mowbray et al in the UK in 1988). Enteroviral RNA was detected in 33% of patients.

- Symptoms observed in ME/CFS are compatible with a viral aetiology.

- Many infectious agents have been cited as implicated in ME/CFS including EBV, Lyme, parvovirus, enteroviruses, Q fever, RRV, mycoplasma and HHV-6.

- Over the last ten years there has been increasing evidence that infection is most likely to be a prime cause of ME/CFS.

**Gastrointestinal dysfunction**

- As noted in the Virology section (above), many ME/CFS patients have persistent or intermittent gastrointestinal symptoms: VP-1 was positive in 80% of patients and enteroviral RNA was detected in a number of stomach biopsies, compared to none in controls

- Professor Kenny De Meirleir from Brussels (but now in the USA) found that 80% of ME/CFS patients exhibit problems with digestion: regular findings of antibodies (IgA, IgM) to intestinal bacteria in the blood of patients indicate disturbance of the gut permeability barrier; this dysfunction results in intestinal bacteria entering the blood stream.

- Professor Kenny De Meirleir also showed that fructose malabsortion is very common in ME/CFS patients and can lead to intestinal dysbiosis; careful diet is therefore required.

**Sleep disruption**

- Nine clinical sleep abnormalities exist in ME/CFS. Actigraphy studies show four main types: hypersomnia; severe insomnia; “tired but wired” (hyposomnia) and delayed sleep.

- Studies by Sieki Tajima from Osaka, Japan, revealed by autonomic analysis in ME/CFS patients that poor sleep may be due to a lack of parasympathetic activity during attempted sleep periods.

- Dr Joan Shaver from the University of Illinois, Chicago, found that there is decreased growth hormone production during sleep.

**Fatigue**

- Various methods to study fatigue were described by Professor Y Watanabe from Osaka, Japan, such as cortical function, autonomic nerve function, biochemical markers in plasma and saliva, and scans of brain function.

- Researchers at De Paul University, USA, have shown there are five types of fatigue associated with ME/CFS.

- Dr Garth Nicolson from the Institute for Molecular Medicine, CA, showed that fatigue is caused by damage to the mitochondria, thus impairing the patient's ability to make ATP and NADH, and Dr Jacob Teitlebaum from Annapolis, Maryland, showed that patients have decreased ATP.

**Pain**

- Pain was described as a major feature in many aspects of ME/CFS. There is a pain matrix in the brain and the experience of pain occurs as a result of central processing via a CNS network. Multi responses may occur in different organs.

**Cognitive impairment**

- J.Alegre-Martin from Barcelona, Spain, studied neurocognitive impairment in ME/CFS and found considerable cognitive deterioration, with a difference in processing between right and left brain hemispheres.

- A study by R Shoemaker (Pocomoke, USA) looked at the systemic inflammation in ME/CFS caused by C4a and suggested that the central nervous system correlates of cognitive dysfunction have an inflammatory basis.

**Immunology**

- There are elevated pro-inflammatory cytokines in patients with ME/CFS. (Cytokines are immunologically-based chemicals that can cause viral symptoms such as sore throat, swollen glands and flu-like symptoms often seen in ME/CFS).

- Brian Gurbaxani and Suzanne Vernon et al (CDC, Atlanta) demonstrated that increased levels of IL-6 correlate well with C-reactive protein (CRP) and are proportionate to symptom severity in ME/CFS.

- Barry Hurwitz from the University of Miami showed that pro-inflammatory cytokines have a secondary effect in reducing red blood cell (RBC) volume, due to probable suppression of RBC production in the bone marrow.

- Studies by Professor Kenny De Meirleir et al (Belgium) found that the majority of ME/CFS patients had increased rates of RNase-L activity (83%), RNase-L fragmentation (88%) and a massive 95% had increased elastase levels. These abnormalities could contribute to the muscle symptoms seen in ME/CFS.

- Mary-Ann Fletcher, a colleague of Nancy Klimas from the University of Miami, found that perforin (a molecule in cytotoxic lymphocytes) is low in ME/CFS, as are NK cells.

- There is increased incidence of thyroid malignancy associated with ME/CFS. Dr Byron Hyde from Canada stressed the importance of evaluating this by thyroid ultrasound and needle biopsy, despite euthyroid serum results.

- Brigitte Evangard from Stockholm, Sweden, found increased levels of Candida albicans in ME/CFS patients (a sign of a disrupted immune system).

- Anthony Komaroff (Professor of Medicine, Harvard) summarised the immune abnormalities that have been demonstrated in ME/CFS. These include activated CD8 (T cells); poorly functioning NK cells; novel findings –seen only in ME/CFS -- of abnormalities of the 2-5A pathway (RNase-L ratio); cytokine abnormalities (pro-inflammatory dysregulation); increased TGF, and 27 times more circulating immune complexes than in controls.

**Neuroendocrine dysfunction**

- Paul Nestadt from Mt Sinai School of Medicine, NYC, used Magnetic Resonance Spectroscopy to demonstrate that lactate is increased and N-acetyl-aspartate (NAA) is reduced in the brain of people with ME/CFS. High lactate levels corresponded with the level of fatigue and were not abnormal in persons with depression or anxiety. These findings are further evidence that ME/CFS is not psychiatric in origin.

- A significant proportion of patients had elevated brain ventricular lactate. Marked differences in hippocampal glutamate helped differentiate between patients with

ME/CFS with and without depression. These differences support neurobiological distinctions between "pure" ME/CFS and CFS with psychiatric co-morbidity.

- The high lactate levels appear to reflect the existence of exhausted cells in the brain.

- The neuro-endo-immune dysfunction in ME/CFS appears to be related mostly to the abnormal activity of glutamate and serotonin, acetlycarnitine, transforming growth factor-$_B$ and interferon.

**Genomics**

- Genomics is defined as the study of the function and interactions of genetic material in the genome, including interactions with environmental factors. Genetics is the study of a single gene.

- Both play a significant role in ME/CFS. Some people have a genetic predisposition: statistical analyses on over 600 people with ME/CFS found that their closest relatives had higher rates of migraine, irritable bowel syndrome, Raynaud's disease, TMJ disorder, osteoarthritis and myalgia.

- A study by Rosemary Underhill from New Jersey looked at the prevalence of ME/CFS in the offspring of mothers with the disease and found that 24% of affected mothers had offspring with documented ME/CFS.
- A Japanese study looking to identify unique gene expression profiles found that being physically exhausted is not an extension of being tired – it elicits a unique response from the body. These researchers found nine genes with altered activity levels in ME/CFS patients, none of which were found in healthy controls 24 hours after exercise. These genes are involved in mitochondrial functioning; neurotransmission; the immune system; metabolism and the endocrine system – a very common cast of characters in gene expression studies in ME/CFS patients.

- Dr Jonathan Kerr from London stated that his gene expression studies are finding three main abnormalities in ME/CFS patients: these involve the immune system, mitochondrial function and G-protein signalling. There are seven genes upregulated in ME/CFS – those associated with apoptosis, pesticides, mitochdonrial function, demyelination and viral binding sites. Kerr mentioned three genes in particular: gelsolin, which is involved in apoptosis and amyloidosis; one that is upregulated by organophosphates, and a mitochondrial gene involved in the demyelination of nerves.

**Paediatrics**

- The new paediatric diagnostic criteria from Professor Jason et al (De Paul University) means there is now a science-based instrument that will be able to correctly diagnose children and adolescents with ME/CFS.

**Behavioural medicine**

- In contrast to the US and countries such as Australia, South Korea, Japan, Sweden, Belgium, Chile, Latvia and Spain (to name just some), the UK Government is resistant to funding any biomedical research into ME/CFS and financially favours studies into behavioural modification regimes for such patients.

- Dr Ellie Stein, a psychiatrist from Canada, was specific about such behavioural modification programmes. Neither ME/CFS nor fibromyalgia is considered a psychiatric disorder. She stated that unfortunately, many medical practitioners conclude erroneously that psychiatric care and vigorous exercise are "the cure" for ME/CFS. Previous CBT/GET programmes were based on the false assumption that avoidance of activity, illness severity and increased attention to symptoms were causing or perpetuating symptoms, when in reality they were the result of the illness. Of seven controlled studies using CBT, only four were positive and most were inconclusive or poorly done. Five studies of graded exercise in ME/CFS patients showed no improvement in pain, sleep, autonomic function, immune system function or cognitive symptoms. Stein emphasised that neither CBT nor GET works well because many ME/CFS patients do not have dysfunctional beliefs, many are already functioning at maximum activity levels, and exercise makes some patients worse. Whilst CBT and GET are the most studied behavioural interventions, results are short lived.

Despite the significant biomedical abnormalities found in ME/CFS that have been published over the last two decades and despite the vast amount of research evidence presented at so many international conferences over so many years and despite the $4.5 million public awareness campaign bankrolled by the US Centres for Disease Control, some clinicians – in this case Peter Manu, Associate Professor of Medicine and Psychiatry at Yeshiva University's Albert Einstein College of Medicine and Director of Medical Services, Hillside Hospital, Long Island Jewish Medical Centre, New York – still refuse to accept the scientific evidence. On 14th February 2007, Manu went on record as affirming: "I personally believe the CDC's emphasis on (ME/CFS) has been wrong from day one. I don't think there is much to it" (The Times, Frankfort, Indiana, 14th February 2007).

There speaks the difference between psychiatry and science.

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**Corrections and Clarifications**

Margaret Williams thanks those who have queried her reference in her article "Facts from Florida" to Dr P Chaney being at he Mayo Clinic.

She wondered about this herself but accepted in good faith the notes of Dr Lesley Ann Fein which clearly stated that Dr Cheney was at the Mayo Clinic.

http://www.cfidsreport.com/News/07-IACFS_Conference_2007_Research_Summary.htm

Margaret also apologises for the numerous typing errors including "peforin" which should of course be perforin and "disarry" which should of course be disarray.

http://www.meactionuk.org.uk