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## Comparison of MRC-funded research and MERGE-funded research into ME/CFS

Margaret Williams (20<sup>th</sup> March 2004)

In November 2003 the UK Medical Research Council (MRC) announced its funding of the PACE trials (Pacing, graded Activity and Cognitive behaviour therapy, a randomised Evaluation) studying those with chronic fatigue syndrome/myalgic encephalomyelitis (“CFS/ME”), for which the entry criteria are to be the Oxford (1991) criteria that were formulated by psychiatrists Michael Sharpe, Peter White and Simon Wessely, among others. The well-known aim of these psychiatrists who have designed a more robust form of Cognitive Behaviour Therapy (CBT) in specific relation to ME/ICD-classified CFS is to change patients’ “aberrant” perceptions” that they are suffering from a physical, not a psychiatric, disorder.

In combination with direct Government funding, these psychiatrists are to receive £11.1 million for more “research” into the claimed benefits of CBT in “CFS/ME” (£2.6 million from the MRC and an additional £8.5 million from Government direct).

The Oxford criteria expressly exclude those with International Classification of Diseases (ICD)-classified ME because in the ICD, ME is classified as a neurological disorder and the Oxford criteria suggest that those with neuromuscular disorders should be used as controls: essentially, the Oxford criteria select patients with idiopathic chronic fatigue, which is not synonymous with ME (ME is synonymous with ICD-classified CFS but not with other chronic fatigue states).

Currently, Peter White is advertising for a PACE Trial Manager at an annual salary of £34,000 (applications to be in by 6<sup>th</sup> April 2004). The background information for applicants states that the project is a “*prestigious MRC funded study of promising new treatments (sic) for a condition of considerable public health importance. The study is innovative in this illness in having a close collaboration with the leading patient charity Action for ME. Other members of the team include Professor Simon Wessely. The Clinical Trials Unit at the Institute of Psychiatry will be leading on database management and analysis*”.

In the Trial identifier itself (the document that was submitted to the MRC for funding approval) it states: “*Subjects will be required to meet operationalised Oxford criteria for CFS. This means 6 months or more of medically unexplained, severe, disabling fatigue affecting physical and mental functions. Compliance with both the treatments and the study will be maximised by the collaboration and support of AfME.....Mr Chris Clark, CEO of AfME, will be a member of the Trial Management Committee*

*(TMC) and help with external relations...staff at the Clinical Trials Unit will be primarily responsible for database design and management, directed by Professor Simon Wessely*". The Trial identifier specifically states that there are no planned analyses of any subgroups of "CFS".

On 10<sup>th</sup> February 2004, in apparent keeping with his remit to deal with "external relations", Chris Clark issued an "Action for ME Statement" in which he said *"I note there has been some comment regarding the criteria for the PACE study. Some time ago the researchers agreed at our request to also record all those in the study against BOTH the Fukuda (CDC 1994) criteria and the operationalised criteria for myalgic encephalomyelitis"*.

This raises three important points:

- (i) in his referral to the PACE trial's "operationalised criteria for ME" Chris Clark seems to be in error since in the Trial identifier, subjects for inclusion "will be required to meet the **operationalised Oxford criteria**" which, by definition, **exclude those with ME** (an ICD classified neurological disorder and as such is specifically excluded from the Oxford criteria)
- (ii) The 1994 CDC (Fukuda et al) criteria specifically state the need for "Essential Subgrouping Variables", together with "Optional Subgrouping Variables", but the PACE Trial identifier confirms that there is to be no subgrouping in the MRC PACE trials
- (iii) for the entry criteria to a study to be changed **after** the study protocol has been rigorously scrutinised and funding has been approved by the MRC is indeed bizarre and raises many further issues that will be discussed by the Countess of Mar in her imminent meeting with Professor Colin Blakemore of the MRC

As Simon Lawrence of the 25% ME Group for the Severely Affected accurately notes in his response to the misleading article ("Capital clinic gives hope to ME sufferers") in the Edinburgh Evening News on 17<sup>th</sup> March 2004: *"there is little or no evidence to support the claim that ME patients will benefit from the highly controversial and hotly contested psychological treatment strategies –cognitive behavioural therapy and graded exercise therapy – proposed by Dr Michael Sharpe. Dr Sharpe may indeed have great success with chronically tired patients but ME is not chronic fatigue and Dr Sharpe knows that only too well"*.

Of concern is the issue as to whether or not the continuance of State benefits for those with ME/ICD-CFS will be contingent upon participation in the PACE trials, since if a patient refuses, s/he may be deemed "not to want to get better", but those with ME/ICD-CFS (as distinct from those with idiopathic chronic fatigue) may refuse to enter these trials because they are rightly unwilling to be made worse by participation. Will the Trial results still claim to be applicable to those with ME/ICD-CFS when in reality the psychiatrists may be studying those with idiopathic chronic fatigue?

The approach of both Government and the MRC is to fund only trials that are addressing a psychosocial dimension of “CFS”, to the exclusion (or even the denial of) the now undeniable biomedical evidence of profound multi-system disease.

By comparison, the small UK ME charity MERGE, based in Perth, Scotland ([www.mereseach.org.uk](http://www.mereseach.org.uk)) is dedicated to funding biomedical research into the causes, consequences and treatment of ME/ICD-CFS. Despite being desperately short of funding and thus having to devote much time and effort to fund-raising instead of to its primary goal of biomedical research, MERGE has achieved far more in furthering the understanding of ME/ICD-CFS since its inception in 2000 than the MRC and Government have achieved in the last 20 years.

On 3<sup>rd</sup> October 2003 MERGE held a Royal Society of Edinburgh Workshop entitled “New developments in the biology of Myalgic Encephalomyelitis / Chronic Fatigue Syndrome”. Speakers were of international renown and included Dr Neil Abbot (Director of Operations at MERGE); Dr Gwen Kennedy (Postdoctoral Research Fellow, Vascular Diseases Research Unit, Department of Medicine, University of Dundee); Dr Vance Spence (Senior Research Fellow, Vascular Diseases Research Unit, Department of Medicine, University of Dundee, Scotland); Professor Jill Belch (Professor of Vascular Medicine at Dundee); Professor Julian Stewart (Director, Centre for Paediatric Hypotension and Professor, Department of Paediatrics and Physiology, Westchester Medical Centre and New York Medical College, USA); Professor Kenny De Meirleir (Professor of Physiology and Medicine, Vrije Universiteit, Brussels, Belgium) and Professor Grahame Hardie (Division of Molecular Physiology, Wellcome Trust Biocentre, University of Dundee).

The following is a highly simplified summary of that Workshop:

Every day in the UK, between 120,000 and 240,000 people with ME waken with debilitating malaise and pain; they remain ill and largely ignored by mainstream academic medicine because in the past, most research effort has gone into the validation of psychosocial management strategies that have practical difficulties and are not curative.

Graded exercise therapy is not universally successful in ME/CFS patients.

Given the inadequacy of current management strategies, there is a pressing need to extend and expand biomedical research programmes.

The human cost of ME is substantial and has not been well reported.

A significant number of people with ME are substantially functionally (ie. physically) impaired.

Between 15% and 20% of patients had changed GP in the past because of a “negative attitude” towards their illness.

The 1994 CDC (Fukuda et al) definition is now widely recognised as having a number of limitations, which include:

- the requirement for all clinical signs to be removed from the definition
- the specificity of the definition is poor, thereby allowing the inclusion of heterogeneous groups of patients (including those with somatoform disorders)
- it makes no attempt to differentiate patients on the basis of severity of illness

A range of abnormalities has been found in ME by a number of different research groups (biochemical, vascular, brain and muscle).

The microvascular research laboratory at Dundee (run by Dr Faisal Khan) has developed a number of methods whereby vascular reactivity can be assessed non-invasively and has carried out experiments relating to the vascular biology of ME/CFS; these have demonstrated that the vascular response in ME/CFS is very unusual and “*is unlike any other disease we have encountered*”: these unusual findings help to explain some of the unusual symptoms that ME/CFS patients experience.

There may be “re-perfusion injury” in ME/CFS patients (a state where vasodilatation that is necessary for the delivery of nutrient is compromised).

Vascular symptoms characterise ME/CFS: research has established that, as far as the general circulation is concerned, oxidative stress and the production of vasoconstrictor and prothrombotic byproducts are central to the pathophysiology of ME/CFS.

Pilot data shows that arterial stiffening is increased in some ME/CFS patients.

Blood vessels of patients with ME/CFS have been shown to be abnormally sensitive to acetylcholine, a most unusual if not unique situation.

Blood flow abnormalities in patients with ME/CFS may be the result of problems with endothelial-generated acetylcholinesterase. The abnormal recovery pattern seen only in ME/CFS patients is suggestive of a disturbance to part of the vascular endothelium and may contribute to the unusual vascular symptoms that are characteristic of the illness.

The central hypothesis is that there is endothelial dysfunction in ME/CFS. Circulating levels of endothelin-1 (one of the most powerful vasoconstrictors) have been shown to be raised in people with ME/CFS (high levels have been reported in myocardial infarction, in diabetes and in HIV infection).

Oxidative stress is the name given to damage caused by free radicals; such damage is implicated in other conditions as well as in ME/CFS, including cardiovascular disease,

most neurological diseases and it may be also be associated with acute and chronic infections, which many believe to be at the root of ME/CFS.

As a direct consequence of post-exercise free radical generation, there may be progressive formation of peroxynitrite, leading to the development of vasoconstrictor isoprostanes. The symptoms of post-exertional myalgia in ME/CFS may be akin to those experienced by the vascular patient with intermittent claudication.

Isoprostane levels (sensitive and reliable markers of oxidative stress) are raised by as much as 40% in ME/CFS patients.

There may be a case for suggesting that ME/CFS is an inflammatory disorder, albeit an unusual one: the Dundee Vascular Unit has found novel evidence that patients with ME/CFS have detectable abnormalities in neutrophils (a type of white blood cell), specifically that there is a larger proportion of apoptotic cells (programmed cell death) than in healthy subjects, consistent with an activated inflammatory process.

**These findings are suggestive of an underlying viral or toxic illness associated with persistent infection and immune activation.**

There is evidence from the literature that orthostatic intolerance (OI) is a substantial problem in ME/CFS. With OI, patients are ill for a long time.

Defining symptoms of chronic OI include day-to-day dizziness in all patients; a high incidence of altered vision; fatigue; nausea; neurocognitive deficits; sleep problems; sweating; palpitations; headaches; tremulousness; difficulty breathing and difficulty swallowing. Patients are often unable to hold down jobs or attend school.

Patients frequently display acrocyanosis (bluish-purple discolouration of the hands and feet due to slow circulation of the blood through the small vessels in the skin) and pooling in their lower extremities: increased venous filling and enhanced microvascular filtration during orthostasis results in pooling. Central hypovolaemia causes reflex tachycardia.

There is a potential link between altered vasoreactivity and antecedent inflammatory disease: such a link has been established in ME/CFS patients in whom orthostatic intolerance frequently occurs.

ME/ICD-CFS is considered to be a disorder of the innate immune system.

Not every case of ME/CFS is of viral origin, but all ME/CFS patients have one of three permutations of immune dysregulation involving ds-RNA-activated protein kinase (PKR) and RNase L (the RNase L pathway is involved in fighting infection). These two proteins are released when infectious agents (mainly viruses) invade a cell, inducing the production of interferons which trigger a defence response that is part of the innate immune system. ME/CFS patients have either (a) PRK dysfunction without RNase L

dysfunction (b) PKR dysfunction *and* an RNase L dysfunction *or* (c) RNase L dysfunction with a minimal PKR dysfunction.

**It is important to note that dysregulation of RNase L and PKR is also found in various autoimmune diseases and is not unique to ME/CFS.**

Deregulation of the (2,5A) synthetase RNase L antiviral pathway in subsets of ME/CFS patients has been extensively reported in the scientific literature.

Elastases and calpain cleave high molecular weight RNase L (83 kDa) into a truncated low molecular weight RNase L of 37 kDa and in ME/CFS there is a wide spectrum of cleavage (a phenomenon also seen in multiple sclerosis patients); such altered RNase L activity profoundly affects cellular physiology, including apoptosis. Cellular RNase L abnormalities are found in monocytes but not in T-cells, and this provides a clue leading to the Th2/Th1 cytokine imbalance seen in ME/CFS.

**An up-regulated RNase L pathway in ME/CFS is consistent with an activated immune state and a role for persistent viral infection in the pathogenesis of the disorder.**

The relationship between these immune dysregulations and clinical manifestations of the illness is probably of the most interest to patients, and there is published evidence that RNase L levels can be related to symptoms seen in ME/CFS.

Of particular relevance is the Canadian case definition for ME/CFS which is based on the Holmes (1988) definition plus ten empirically identified symptoms which include paralysis, new sensitivity to foods and drugs, cold extremities, gastrointestinal symptoms, difficulties with words and fasciculations.

**An understanding of these abnormalities at the molecular level and sub-stratification of patients is essential for the development and identification of effective therapeutic strategies.**

Findings support the view that there may be several distinct subgroups of ME/CFS and that these subgroups urgently need to be more clearly defined.

**[ By contrast, in the UK there is to be no study of subgroups by Government-funded research, nor any research into the pathoetiology of the disorder. In his furious reaction to the 2001 paper by Professor Malcolm Hooper and Sally Montague entitled “Concerns about the forthcoming UK Chief Medical Officer’s Report on Myalgic Encephalomyelitis (ME) and Chronic Fatigue Syndrome (CFS), notably the intention to advise clinicians that only limited investigations are necessary” Dr Charles Shepherd (in his dual role as then Medical Adviser to the ME Association and member of the Key Group of the CMO’s “independent” Working Group on CFS/ME) wrote on 17<sup>th</sup> July 2001 to the Chief Medical Officer in the following terms: *“I acknowledge that I have opposed the inclusion of testing for RNase L activity (because) all the published information so far comes from researchers who***

***have a financial interest in their promotion – a situation which involves a clear conflict of interest***. In the CMO's Working Group Report, Professor Tony Pinching was equally opposed to the studying of sub-groups ].

Given the work of MERGE, what possible justification can the MRC and Government have for continuing to ignore the pleas for more funding into the biomedical aspects of ME/ICD-CFS, whilst continuing to fund yet more psychiatric "research", the aim of which is to deny the physical reality of such a uniquely complex organic disorder?