

Can the MRC PACE Trial be justified

Margaret Williams 17th December 2009

In March 2003 the House of Commons Select Committee on Science and Technology produced its Report "The Work of The Medical Research Council" (HC 132) in which MPs issued a damning judgment on the MRC, lambasting it for wasting funds and for introducing misguided strategies for its research. The Select Committee had received seven representations about the MRC's refusal to heed the biomedical evidence about ME/CFS. MPs found evidence of poor planning and of focusing on "politically-driven" projects that have diverted money away from top-quality proposals. The unprecedented attack was the result of a detailed probe into the workings of the MRC. In particular, MPs questioned why the MRC was content to support policies and projects that are likely to perpetuate such criticism.

Given that biomedical research, including gene research (which has shown that in people with ME/CFS, there are more gene abnormalities present than are found in cancer sufferers) has demonstrated that the psychiatrists who hold such sway at the MRC are comprehensively wrong about ME/CFS, nowhere could such criticism be more apposite than in relation to the PACE Trial.

Patients with ME/CFS and their families are in despair, because no-one in authority in the UK seems to be listening: as Mike O'Brien MP, Minister of State for Health, made plain at the APPGME meeting on 2nd December 2009, Ministers can no longer tell agencies of State what to do. This apparently means that, no matter what conclusions are arrived at or what recommendations are made or what evidence is put before a Minister, the Minister concerned can deny having any power to implement change. The Minister himself is reported to have said that he could not require the MRC to undertake research in any specific field, nor could he require Primary Care Trusts to follow Ministerial command. As far as ME/CFS is concerned, it seems that there is nothing the Government can -- or will -- do about the current situation.

It is apparent that the Government feels no duty of care towards those whose life has been devastated by ME/CFS, a situation that is borne out by Professor Stephen Holgate's confirmation at the Royal Society of Medicine Meeting on 11th July 2009 (Medicine and me; hearing the patients' voice) that the Government will not permit integrated research into ME/CFS.

This can only mean that the influence of the Wessely School over the lives of people with ME/CFS will continue and that their tactics of denial will remain unchallenged, no matter what the calibre of the biomedical evidence showing them to be wrong. As people recently drily commented on an ME group, those tactics include:

"load up your committees with your biased friends and pretend they are offering a fresh look; give really negative scorings to biomedical applications; try to stop biomedical papers getting published in the better known journals; make sure to keep on publishing psychiatric rubbish to bias the general medical population and scientific community against any other explanation, and give the impression that CBT/GET is all that is needed i.e. no need to waste all that money on silly biomedical projects" (LocalME@yahoogroups.com 6th December 2009) and

"ensure you use the sketchiest diagnostic criteria you can get away with; wherever possible, avoid seeing / talking to patients at all; never discuss / involve the severely affected; avoid using objective outcome measures; rotate the name of lead authors on papers and ensure you include plenty of reference papers from your psychosocial mates...." (LocalME@yahoogroups.com 7th December 2009).

As others have noted, the strategy is (1) to ignore ME; (2) to ensure that CFS is seen as a problem of false perception, then (3) to reclassify "CFS/ME" as a somatoform disorder (Co-Cure NOT:ACT: 12th January 2008), which is far removed from the reality of ME/CFS, the CNS dysfunctions of which are described by Dr Byron Hyde as being caused by "widespread, measurable, diffuse micro-vasculitis affecting normal cell operation

and maintenance....The evidence would suggest that ME is caused primarily by a diverse group of viral infections that have neurotropic characteristics and that appear to exert their influence primarily on the CNS arterial bed" (ibid).

Patients and their families, many clinicians and researchers are well aware of such strategies and tactics but -- so powerfully has the Wessely School myth about ME/CFS been promulgated -- have been unable to halt them.

As Dr Jacob Teitelbaum reported, the XMRV virus study clearly documents that (ME)CFS is validated within the mainstream medical community as a real, physical and devastating illness, *"again proving that those who abuse patients by implying that the disease is all in their mind are being cruel and unscientific...Though the economics may cause a few insurance companies to continue to unethically deny the science, so they can avoid paying for the health care and disability costs they are responsible for, this research should speed up understanding of the illness. Meanwhile, for those with the illness, their families and their physicians, it is now clear that this is a real and devastating illness"* (Co-Cure RES: 4th December 2009).

There can be no doubt that, for patients with ME/CFS as distinct from those suffering from chronic "fatigue", neither CBT nor GET is effective, otherwise everyone would by now be cured.

How, for instance, does the Wessely School's "CBT model of CFS" accord with the fact that in the South African epidemic, all the rats that were injected with the urine of ME patients died, but not a single rat died that was injected with the urine of controls? The Wessely School's answer is likely to be that "epidemic ME" is not the same as present day "CFS/ME", an explanation that does not withstand scrutiny, given that the only symptoms of "CFS/ME" on which the Wessely School focus are those that are known to occur in mental disorders (tiredness, anxiety, depression and mood disorders, the latter being a consequence, not a cause, of ME/CFS), whilst ignoring, dismissing or wrongly attributing symptoms such as vertigo, post-exertional physiological exhaustion, intractable pain, neuromuscular in-coordination and dysautonomia to "hypervigilance" to "normal bodily sensations", a situation best described as iatrogenic abuse.

As clinical psychologist Carl Graham recently pointed out, the type of CBT *"used in psychoneuroimmunological interventions is not limited to changing 'irrational beliefs' "*, noting: *"The view that all those involved with CBT based treatments accept the idea that irrational thinking had led to a somatoform disorder in a patient who has a chronic disease is entirely unfortunate"* (Co-Cure NOT 14th December 2009) and in an update (Co-Cure 15th December 2009) the same psychologist referred to *"the association of CBT with the very unfortunate tendency of some in the treatment field to claim ME/CFS is a somatoform or psychiatric disorder"*, concluding that he was *"not advocating for CBT based practices for chronic health problems to continue where they are being done poorly or as a monotherapy"*.

To change what they regard as "irrational beliefs" of people with "CFS/ME is, however, the expressed intention of the PACE Trial Investigators, who continue to promote CBT/GET as a monotherapy for "CFS/ME", a matter of concern to experts such as Dr David Bell from the US, who on 12th December 2009 was quoted in The Daily News online (<http://bit.ly/4KofDR>): *"The tiredness linked to (ME)CFS is caused by a reduction of blood flow to the brain' Bell said. The doctor said the blood flow in people with severe cases of (ME)CFS can be as low as people with terminal heart disease"*. Would people with terminal heart disease be required to undergo psychotherapy to convince them they are not in fact sick, but only believe that they are sick?

The apparent intention of the PACE Trial Principal Investigators to remove people with ME/CFS from receipt of state and insurance benefits raises a larger question than just welfare reform. It is also about the way illness is being redefined and reclassified and about why this is happening and about what forces are at work in this process of redefinition.

As recently noted by Overton (Psychological Medicine 2010;40:172-173; online 08.10.09), in Sharpe et al's 2009 study (Neurology out-patients with symptoms unexplained by disease: illness beliefs and financial benefits predict one-year outcome), one of the authors (Stone) accepts that terms such as 'functional

weakness' may well need to be re-worded as 'conversion disorder' on official documents. Challenging Sharpe's assertion that their data lend "support to the idea that interventions which change these variables [ie. state benefits or opposition to physician-imposed psychological explanations of physical symptoms] may improve the outcome for this patient group", Overton points out that Sharpe et al inadvertently infer that patients with "symptoms unexplained by disease" are guilty of benefit fraud and Overton states that it is erroneous for Sharpe to use data in the way he does to assert that "Illness beliefs and financial benefits are more useful in predicting poor outcome than the number of symptoms, disability and distress". Moreover, Sharpe's assertion contrasts with the evidence of Rosata & Reilly who, unlike Sharpe, correlate the level of benefit with the degree of disability (Health & Social Care in the Community 2006:14:294-301).

In their Editorial in the Journal of Psychosomatic Research (Is there a better term than 'Medically unexplained symptoms?' 2010:68:5-8, Epub ahead of print), two of the MRC PACE Trial Principal Investigators, Professors Sharpe and White, clearly state their intention to claim medically unexplained symptoms (MUS -- in which they include ME/CFS) as psychosomatic disorders by stating that the term "functional somatic disorder" fulfils most of their own criteria for re-branding somatoform disorders (those categories being "bodily distress or stress syndrome", "psychosomatic or psychophysical disorder", and "functional syndrome or disorder"). Sharpe and White et al continue: "All too often, these patients receive one-sided, mostly purely biomedical...treatments....Although some existing treatment facilities include both biomedical and psychological therapies...they are not appropriate for ...the majority of patients with the type of symptoms with which we are concerned here. Therefore, some specific treatment facilities have been developed (eg. Chronic Fatigue Clinics in the UK)....The terms...'psychosomatic' or 'psychophysical' are helpful in providing a positive explanation of the symptoms...Alternatively, the term 'functional somatic syndrome' allows explanations...in terms of altered brain functioning...demonstrating that the symptoms are 'real' and yet changeable by alteration in thinking and behaviour as well as by a psychotropic drug".

There could be no clearer confirmation that the UK "CFS" Clinics allegedly for patients with ME/CFS that were set up under the guidance of Professor Anthony Pinching were and remain intended to change patients' thinking and behaviour, which vindicates the countless patients whose damaging experiences and legitimate concerns have been collated by Research into ME (RiME NHS Clinics Folder -- www.erythos.com/RiME).

As noted by Horace Reid (<http://www.meactionuk.org.uk/Wessely-axis.htm>), seventeen years after the 1992 CIBA Symposium on CFS, members of the Wessely axis are still promoting their agenda identified in the secret MRC document in which that Symposium was summarised (<http://www.meactionuk.org.uk/The-MRC-secret-files-on-ME.htm>).

For example, in a 2008 paper comparing "chronic fatigue" in Brazil and Britain, Cho and Wessely et al could not have been more explicit: "British patients were more likely to be a member of a self-help group and to have had sick leave / sickness benefit because of CFS, variables claimed to predict poor outcome...**The greater public and medical sanctioning of CFS/ME and the more favourable economic climate in the UK may lead to greater access to sick leave / benefits for patients with chronic fatigue....There is also evidence of an association between the so-called 'secondary gain' and health outcomes....Therefore, the higher availability of sick leave / sickness benefit because of CFS in the UK may both contribute to and reflect the greater 'legitimisation' of chronic fatigue as a medical disorder**" (Physical or psychological? A comparative study of causal attribution for chronic fatigue in Brazilian and British primary care patients. Acta Psychiatr Scand 2008;118:1-8). Reid noted how the article reflected the MRC-funded PACE Trial of CBT and GET as set out in the Trial Protocol that was published in BMC Neurology (2007;7:6): "Predictors of outcome: Predictors of a negative response to treatment found in previous studies include...membership of a self-help group, being in receipt of a disability pension, focusing on physical symptoms and pervasive inactivity" (3,18,19).

There is no mention in that paper of on-going viral infection but, perhaps expediently, in a paper that came out about the same time as the XMRV news broke, Wessely quietly inserts his own new model that allows for infection as a perpetuating factor, so the Wessely School goal-posts may be subtly shifting: "...a model of

the aetiology of CFS can be constructed from a combination of pre-morbid risk, followed by an acute event leading to fatigue, and then a pattern of behavioural and biological responses contributing to a prolonged severe fatigue syndrome. Based on this model, the initial cause of the fatigue has a limited impact on the eventual course of the illness....However, there is emerging evidence which suggests that it may be appropriate to extend it to encompass fatigue with an apparent medical cause....it may be that the divide between fatigue secondary to diagnosed medical problems and CFS may need to be made more permeable" (Chronic fatigue syndrome: identifying zebras among the horses. Samuel B Harvey and Simon Wessely. BMC Medicine 2009;7:58).

This is very different from the PACE Trial concept of "CFS/ME" which, in over 2,000 pages of information obtained under the Freedom of Information Act, including all the Manuals, does not allow for any on-going pathology.

Because ME/CFS is a targeted disorder for the withdrawal of state benefits, the situation for ME/CFS patients in the UK is increasingly dire, with severely affected patients being harassed by the Department for Work and Pensions requiring a 60-page booklet to be completed because the DWP menacingly informs such patients: *"We have reason to believe that you are capable of work"*.

An article entitled "Mistaken Illness Beliefs..." by David Lees published in the ME Association's magazine "ME Essential" (Winter 2009: 34-35) admirably captures the situation:

"...a friend with ME...was told, despite the persistence of her symptoms, that the only thing preventing her full recovery was her 'mistaken illness beliefs'....'But doctor, I still have nausea / muscle pain / severe weakness / headaches / exhaustion etc' can all be met with 'It's just your illness beliefs. There's nothing else wrong, and if you still experience symptoms, it's because you haven't got your beliefs right yet. As soon as you do, you'll be well'....It's impregnably self-immunised (referring to Sir Karl Popper's 'self-immunisation' theory which showed that such theories are scientifically worthless because they have no real explanatory or predictive power) and therefore scientifically worthless as a diagnosis.....(Referring to researchers who are struggling to uncover complex mechanisms and to answer difficult and involved questions, Lees continues): Uncertainty and humility are appropriate attributes in these circumstances and they seem noticeably lacking in much of the psychological approach to diagnosis and treatment of ME.....Doctors are presented with difficult, confused, uncertain data and interpretation can be very difficult; but surely this is an argument for more caution and admissions of uncertainty rather than a reason to make scientifically dubious statements with Olympian self-certainty...In the absence of proper research evidence, to work from the assumption that the illness is not primarily organic in origin and must therefore be primarily psychological is unscientific...We should surely have moved on from filling gaps in our medical knowledge with assertions...the least we should expect from medical practitioners in the NHS, whose diagnosis profoundly affects the lives of those with ME, is that their methods and conclusions should be scientific. The diagnosis of 'mistaken illness beliefs' is not – it is itself merely a statement of belief".

Given the significant opposition to the PACE Trial from many quarters, including both patients and professionals and also including the ME Association (the oldest ME charity) and, it is understood, from many patient members of the charity Action for ME (though not the charity's Trustees, who support the PACE Trial, which seems to indicate that AfME is not a patient-led organisation), there are compelling grounds for suggesting that the PACE Trial should never have been granted approval or funding.

The ME Association has been adamant that the PACE and FINE trials should be halted and on 22nd May 2004 posted the following on its website (which was printed in its magazine "ME Essential" in July 2004):

"The MEA calls for an immediate stop to the PACE and FINE trials

"A number of criticisms concerning the overall value of the PACE trial and the way in which it is going to be carried out have been made by the ME/CFS community. The ME Association believes that many of these criticisms are valid. We believe that the money being allocated to the PACE trial is a scandalous way of prioritising the very

limited research funding that the MRC have decided to make available for ME/CFS, especially when no money whatsoever has so far been awarded for research into the underlying physical cause of the illness. We therefore believe that work on this trial should be brought to an immediate close and that the money should be held in reserve for research that is likely to be of real benefit to people with ME/CFS. We share the concerns being expressed relating to informed consent, particularly in relation to patients who are selected to take part in graded exercise therapy. The Chief Medical Officer's Report (section 4.4.2.1) noted that 50% of ME/CFS patients reported that graded exercise therapy had made their condition worse, and we therefore believe that anyone volunteering to undertake graded exercise therapy must be made aware of these findings".

The ME Association notice additionally called for all further work on the FINE trial to be halted, saying the MEA *"is not convinced by the evidence so far put forward in support of this approach"*.

It is recorded in documents obtained under the Freedom of Information Act that the Principal Investigators and the various Ethics Committees were fully aware of the strength of the opposition to the PACE Trial but that these were dismissed by Professors Sharpe and White: Minutes of the Joint Trial Steering Committee and Data Monitoring and Ethics Committee meeting held on 27th September 2004 record that Professor Paul Dieppe (Chair of the Data Monitoring and Ethics Committee) expressed: *"anxiety that recruitment might be impeded by the anti-PACE/FINE lobbyists. Professor Sharpe and Professor White stated that lobby groups had not previously affected recruitment in trials of GET, which is the most controversial of the therapies to be tested"*.

A further example is to be found in the Report of the PACE Trial statistician Dr Tony Johnson (a member of the Trial Management Group, a member of the Trial Steering Committee and the person who will oversee the Clinical Trial Unit that is directed by Professor Wessely) who confirmed in the MRC's Biostatistical Unit's Quinquennial Report for 2002 – 2006 that the MRC was funding the PACE and FINE Trial *"despite active campaigns to halt them"*. A notable point is that his Report was co-authored by Professors Peter White, Trudie Chalder and Michael Sharpe, so all of them were aware of the strength of opposition to the PACE Trial.

It is also a matter of record that Principal Investigator Professor Michael Sharpe confirmed: *"The MRC is currently funding the PACE trial...However, the trial has faced serious antagonism from some, but not all, patient groups, mainly because of concerns about the use of 'psychological treatment' for a condition that is seen by many as a medical disorder"* (Report on MRC Neuroethics Workshop, 6th January 2005: Section 2: Altering the brain).

It is certainly the case that even the MRC's own Neuroethics Committee expressed doubts over the use of CBT: *"...CBT aims to influence how a person thinks or behaves...Although psychotherapies are usually thought of as psychological therapies, there is increasing evidence that they can alter brain function. **Further research is needed to ...determine whether therapies are reversible or if there are persistent adverse effects.** There is already evidence that in certain situations psychotherapy can do harm...**There is also increasing public concern that psychological therapies could be used for brainwashing.**...How much information should patients be given about the possible effects of therapy on their brain?...CBT techniques are now being used more widely to treat somatic conditions...How appropriate is this use of psychological therapy?*

In an article in the New York Times that was published before the PACE Trial began (27th August 2002: "Behaviour: Like Drugs, Talk Therapy Can Change Brain Chemistry"), Richard Friedman MD – a psychiatrist who directs the Psychopharmacology Clinic at the New York Weill Cornell Medical Centre – stated *"Psychotherapy alone has been largely ineffective for diseases where there is strong evidence of structural, as well as functional, brain abnormalities. **It seems that if the brain is severely disordered, then talk therapy cannot alter it"**.*

As there are structural brain abnormalities documented in the ME/CFS literature since at least 1992, one of which being the significant loss of grey matter in the brain with irreversible loss of grey cells, especially in

Brodmann's area 9, (which may indicate major trauma to the brain), then the chance of cognitive behavioural therapy being effective in ME/CFS is probably zero.

Indeed, it was reported by Professor Leonard Jason at the Reno Conference (March 2009) that one group of patients did not benefit from cognitive behavioural interventions: this was the subset whose laboratory investigations showed they had increased immune dysfunction and low cortisol levels.

As the data discussed by Friedman was known about in 2002 (the same year that the UK CMO's Working Group Report was published), then it must be asked why this knowledge has been disregarded by the Wessely School psychiatric lobby.

Given what is already known about the inherent dangers of CBT/GET for those with ME/CFS (especially the known effects of graded exercise as an inducer of oxidative stress and the effects of incremental aerobic exercise on the cardiovascular problems known from the early part of the twentieth century to be an integral feature of authentic ME/CFS), on what ethical grounds can those already crushed by such a heavy illness burden as that imposed by ME/CFS be subjected --- despite denials, in some cases by apparent deceit and coercion -- to a management regime that seems to have no hope of beneficial results?

This raises once again the disturbing question: in whose best interests is the MRC PACE Trial being undertaken?

At the MRC Workshop on CFS/ME held on 19th / 20th November 2009 at Heythrop Park, Oxfordshire, in his introduction Professor Stephen Holgate effectively said that the reason for the meeting was the need to move forward, **to get away from old models and to use proper science**, and that there was no reason not to change things, a view he had also expressed at the RSM meeting "Medicine and me" on 11th July 2009.

The question is -- will the results of the MRC PACE Trial and the vested interests of the Wessely School ever permit the getting away from "*old models*"?

The science is there, the evidence is there, but the political will still seems not to be there, and until the Government can no longer credibly refuse to permit such change, Holgate's hopes are unlikely to materialise in the UK.