So near yet so far – from Mission Accomplished?

Margaret Williams **7th September 2010**

The British Association of CFS/ME (BACME, of which Dr Esther Crawley is Chair) supports the current NICE Guideline CG53 and its recommendation of only cognitive behavioural therapy and graded exercise in the management of ME/CFS. BACME has taken on the role of training NHS staff accordingly, even though it seems to be accountable only to itself; it is to hold a meeting on 13th-14th October 2010 at Milton Keynes and its provisional programme affirms that Professor Peter White (Chief Investigator of the MRC PACE Trial on ME/CFS) will speak about it in a talk entitled "***PACE trial: so near yet so far***". The BACME notice goes on to say that if the PACE Trial outcome results are not published by then, Professor White will present the design, progress and baseline data from the trial.

From over 2,000 pages of information obtained under the Freedom of Information Act, much is already known about the design and progress of the PACE Trial (http://www.meactionuk.org.uk/magical-medicine.htm), including the fact that its entry criteria were intentionally broad (*"We chose these broad criteria in order to enhance generalisability and recruitment";* Trial Identifier 3.6). Despite the use of such broad entry criteria, there were serious recruitment difficulties, so the entry criteria were broadened even further when on 14th July 2006 Peter White sought approval from the West Midlands MREC to write to GPs imploring them to send anyone with "*chronic fatigue (or synonym)"* for entry into the PACE Trial, thereby opening the trial to anyone who was merely chronically tired.

Given the customary requirement for study cohorts to be as homogeneous as possibly, this seems to defy logic: how can the Wessely School's long-held desire to *"clarify the role that psychiatric disorders have in fatiguing illness"* (Ann Int Med 1994:121:12:953-959) and their inclusion of persons with psychiatric disorders possibly restore to health people with the neuroimmune disease ME/CFS who are allegedly the subjects under study, any more than it would be able to restore to health people with multiple sclerosis or motor neurone disease?

The fundamental point is that the PACE Trial interventions are not designed to offer psychological support to those coping with life-shattering disease, but to comprehensively disabuse them of their belief that they suffer from a serious organic disease. If the aim of the PACE Trial is merely to indulge the Wessely School psychiatrists' unproven beliefs (which Professor Michael Sharpe has already admitted are*"without theoretical foundation"* (http://www.meactionuk.org.uk/The-MRC-secret-files-on-ME.htm), on what grounds did it gain ethical approval?

How can the results of a trial that was deliberately designed to conflate people with behavioural disorders, idiopathic fatigue, fibromyalgia and people with ME/CFS (characterised by immunological, neurological, metabolic, cardiovascular, respiratory and musculo-skeletal dysfunction, the cardinal symptom being post-exertional exhaustion accompanied by malaise) be equally applicable to and effective for such diverse disorders?

If the role of psychiatric morbidity in *"fatiguing illness"* is being studied, then why was the trial designed to exclude people with multiple sclerosis who definitely experience profound and disabling fatigue?

The answer, of course, is that the PACE Trial limits the study to those people suffering from disorders that the Wessely School deem to be "mental" disorders.

Notably, in an exchange of correspondence (Conversing with Professor Simon Wessely: (http://livingwithchronicfatiguesyndrome.wordpress.com/2010/08/29/conversing-with-professor-simon-wessely-part2/), Wessely states: "*…it is essential in any study to make it clear exactly where your subjects come from – without that it is impossible to generalise from any report/paper/treatment. This not a new observation – you will see that we pointed that out in 1996, and have continued in all papers to make that distinction abundantly clear".*

Many would challenge Wessely's assertion that his study cohorts have always been strictly defined; moreover, is it not curious, given that he is in charge of the Clinical Trials Unit for the PACE Trial, that Wessely apparently saw no need to exercise such care in the PACE cohort? Does this not mean that, on Wessely's own admission, if a cohort is heterogeneous (which the PACE Trial undoubtedly is), then the conclusions cannot be generalised and so will have no clinical relevance and thus be a waste of tax-payers' money?

It has already been shown that the PACE Trial Investigators apparently did not adhere to good research practice on numerous other counts also, including their apparent failure to observe either the AGREE Instrument or the Declaration of Helsinki, and there are consequential concerns about how meticulously they will adhere to the CONSORT Statement. CONSORT (Consolidated Standards of Reporting Trials) was developed by a group of scientists and editors in 1996; it was updated in 2001 and again in 2010 and it consists of a checklist that authors are recommended to use for reporting a randomised controlled trial (RCT). It is based on the premise that *"The whole of medicine depends on the transparent reporting of clinical trials"* and its authors note that trials with inadequate methods are associated with bias, especially exaggerated treatment effects, and that reporting is not only often incomplete but also sometimes inaccurate. They point out that: *"Biased*

results from poorly designed and reported trials can mislead decision making in health care at all levels, from treatment decisions for a patient to formulation of national public health policies….Bias jeopardises even RCTs, however, if investigators carry out such trials improperly…The methods used should be complete and transparent so that readers can readily differentiate trials with unbiased results from those with questionable results….We encourage peer reviewers and editors to use the CONSORT checklist to assess whether authors have reported on these items" (D Moher / D. Altman et al; BMJ 2010:340:c869). One of the items on the CONSORT checklist relates to trial design, with particular emphasis on important changes to eligibility criteria that are made after trial commencement (as occurred in the PACE Trial) – and the reasons for them.

Furthermore, as an experienced member of a Research Ethics Committee who is familiar with the PACE Trial documentation has pointed out, the PACE Trial is a classic example of over-measurement of variables (ie. it measures too many variables so it is almost inevitable that the data will show spurious "positive" results which in fact have no clinical meaning).

These are very serious matters that, as Chief Investigator, Professor White will need to address with total transparency sooner rather than later.

In response to a previous formal complaint about the PACE Trial made in 2004 by a former MRC grant-holder, Elizabeth Mitchell, MRC External Communications Manager, wrote on 15th November 2004 about the PACE and FINE Trials: "*The design of these trials have been judged by international and UK peer review to be appropriate for delivering the trial objectives, including use of the broad inclusion criteria".*

This is undoubtedly so, because if a proposal is sent for peer review to those who hold similar views to the Investigators, those reviewers will obviously support it. The real question is – what exactly were the*"trial objectives"*? It was already known that the interventions used in the trial are at best of little help and at worst are damaging to those with ME/CFS (ie. the alleged target group) and that the interventions being studied do not reduce either fatigue or disability in such patients. Was this in reality an elaborate exercise for the benefit of the DWP and the medical/permanent health insurance industry?

It is notable that Dr Cathie Sudlow, an Edinburgh neurologist who collaborates with Professor Michael Sharpe, wrote in the BMJ (BMJ 2010:340:c1260) about the discovery of the retrovirus XMRV in relation to ME/CFS in the Lombardi/Mikovits et al paper that was published in Science on 9th October 2009: "*The role of reviewers here is crucial…their contribution should be publicly recognised and valued by journals and by the scientific community as part of the scientific record.* ***This can surely only happen if reviewers are always openly identified and their comments***

published"(emphasis added). Indeed, but will this apply to the PACE Trial? Would it expose bias if so?

Given the recent findings of the *"dramatic association"* of a family of retroviruses with ME/CFS that have been published in both Science and PNAS (http://www.meactionuk.org.uk/Memo-to-NICE.htm), on what logic or evidence do the PACE Trial Principal Investigators Professors Peter White, Michael Sharpe and Trudie Chalder continue to rely to support their belief that the Trial will confirm that "*behavioural restructuring*" can cure such seriously sick patients (this is what the Trial manuals claim: http://www.meactionuk.org.uk/magical-medicine.htm)? If the PIs do not hold such views, then why have they received £5 million to test those beliefs?

"*So near yet so far":* is it the case that the Wessely School were so near to achieving their goal of showing that ME/CFS is a somatisation disorder, using the PACE Trial data, only to be thwarted by the publication of papers in Science and PNAS showing a strong association of a retrovirus with ME/CFS, making their goal scientifically untenable?

Notwithstanding, the way seems to be being paved by the Wessely School for further disparaging attacks on those scientists who have found retroviral involvement in some ME/CFS patients and for yet more dismissal of the significance of those findings.

Whilst the ground-breaking retroviral link published in PNAS on 23rd August 2010 was announced in over 150 outlets world-wide, including Russia and Latvia, and whilst it was deemed to be of such importance that it featured on the front page of the Wall Street Journal, the UK media remained deafeningly silent and there was effectively a news black-out. It was not until after 31st August 2010 that the Science Media Centre (through which all UK media announcements about medical/scientific issues must now seemingly pass, and where Professor Simon Wessely is a member of the Scientific Advisory Panel) published a statement (apparently back-dated to 23rd August 2010) that downplayed the significance of the retroviral association with ME/CFS.

Entitled "*Expert reaction to PNAS study on viral sequences found in blood of chronic fatigue patients"* and quoting two UK virologists (Professors Robin Weiss and Myra McClure), the SMC press release was dismissive: Professor Weiss stated: "*It is based on small numbers….Let's hope it is not another claim like MMR…which didn't hold up* (untrue: the UK High Court recently ruled that the MMR vaccine is not safe, which the UK Government has been forced to concede: Sunday Times, 29th August 2010)*, but I am sceptical of the claim…One should also bear in mind that no less than 4 negative reports on this topic (failing to find a retrovirus link) have been published this year from reputable groups in the UK, the Netherlands and at the Centre for Communicable Diseases & Prevention in Atlanta, USA"* and Professor McClure stated: "*…it is important to realise that this group*

have not detected the virus (XMRV) that claimed media attention after the publication of Lombardi's paper in Science last year. They describe murine leukaemia virus (MLV)-related sequences that are genetically distinct from XMRV….Several other groups (including Professor McClure's own group)*…have employed the same experimental protocol, yet have consistently failed to detect any retrovirus in CFS patients".*

The SMC has an established track record of down-playing any association of retroviruses with ME/CFS (for example, http://bit.ly/90PAXp and http://bit.ly/aj27AK). Given the disparaging tone of the latest SMC press release, it is little wonder that the UK media did not bother, even belatedly, to publish anything about it. It is possible that the SMC's intention was to ignore the game-changing discovery entirely, but after it was publicly asked by a contributor to an internet group why this important breaking news had not been mentioned except for a low-key article in the Daily Mail, the SMC perhaps felt obliged to note it, but did so as dismissively as possible.

Could this be because nothing is to be allowed to detract from the PACE Trial findings that cognitive restructuring – including graded aerobic exercise -- are likely to be claimed to be restorative for patients with ME/CFS?

It is interesting that, over the years, Professor Wessely has repeatedly asserted that he is no longer involved with the politics of CFS research, most recently at the beginning of August 2010 (http://livingwithchronicfatiguesyndrome.wordpress.com/2010/08/29/conversing-with-professor-simon-wessely-part2/), yet at the first sign of a significant threat to his model from the Whittemore Peterson Institute, he rushed out a paper co-authored by Professor Myra McClure that claimed effectively to negate the WPI findings.

In the same series of correspondence, Wessely states on the record: "*At the time of writing I can say with my hand on my heart that I believe that the treatments that we recommend and use in our clinic are currently the best there is – and nothing i have seen, or read about, suggests otherwise"*. Retroviral involvement in ME/CFS notwithstanding, might this be taken to indicate what the PACE Trial results will conclude?

This firm statement from Professor Wessely (ie. that nothing he has seen or read suggests other than that his favoured behavioural interventions are the best treatment for ME/CFS) seems to indicate that, as noted by the person from Australia who posted the very revealing exchange of correspondence, Wessely's comments are a classic case of the Semmelweis reflex, defined as "*the tendency to reject new evidence that contradicts an established paradigm"*, and s/he commented about Wessely's stance: "*Science works by new evidence replacing existing paradigms. When this new evidence is presented, it is a fallacy to reject it with the argument that it interferes with an*

existing paradigm…if all scientists used Wessely's logic …then there would be no new scientific discoveries". Wessely maintains that the XMRV research fails to model the role that childhood abuse, psychological factors and other infections may play in the illness, whilst also confirming that for the last 21 years he has promoted his own theory that the "cognitive behavioural model" is a better explanatory model for chronic ME/CFS than the chronic viral paradigm that dominated at that time (and which many believe he was instrumental in suppressing).

That patients with ME/CFS have been left with no alternative but to suffer from on-going viral illness for the last 21 years and have been deprived of essential financial support because of the dominant influence of certain psychiatrists is deplorable and may be recorded in future annals of medicine with abhorrence and disbelief.

A recent internet post by "XMRV Global Action" announcing that Francis Collins, Director of the US National Institutes of Health (who oversees an annual budget of more than $31 billion) is to open the First International XMRV/MLV Conference on 7th September 2010 noted that this means the NIH are taking XMRV/MLV very seriously indeed, and that there is an element of potential scandal, given that people with ME/CFS have been complaining of profound viral symptoms for decades (and dropping dead from viral cardiomyopathies and rare lymphomas) while being derided as hypochondriacs (http://www.facebook.com/home.php#!/pages/XMRV-Global-Action/216740433250?ref=ts).

Yet more evidence has emerged in the UK that the Wessely School's various attempts to neutralise what they may consider to be inconvenient findings simply do not withstand logical analysis and their contemptuous dismissal of the biomedical research will no longer carry any weight, because their "cognitive behavioural model" has been dealt what may be a fatal blow.

Whilst there are no children involved in the PACE Trial, paediatrician Dr Esther Crawley is about to start a study looking at the effect of the Lightning Process on children aged from 8 to 18 to see if sufferers can be trained to think differently about how ill they feel and so increase their exercise levels, but an article in the current issue of the American Medical Associations' journal "Archives of Paediatrics and Adolescent Medicine" 2010:164(9):817-823 (Biochemical and Vascular Aspects of Paediatric Chronic Fatigue Syndrome/Myalgic Encephalomyelitis; G. Kennedy et al:) shows how unsuitable such a study may be.

There are thought to be about 15,000 children in the UK with ME/CFS and a team from Dundee that was funded by ME Research UK (MERUK) and The Young ME Sufferers (TYMES) Trust has found abnormalities in the blood of all the children with ME/CFS tested but not in controls, the results

being similar to those previously found in adults with ME/CFS and consistent with an activated inflammatory process.

Professor Jill Belch from the Vascular and Inflammatory Diseases Research Unit, Ninewells Hospital and Medical School, Dundee, explained this new research on the BBC Radio 4 Today programme on 7th September 2010, saying that they have demonstrated two important findings, the first being an abnormal level of an inflammatory chemical in the blood and that this is matched by abnormal white blood cell behaviour; she explained that this is important because *"finding an abnormality is halfway to finding a treatment"*. The second finding, said Professor Belch, is that ME/CFS **is** a physical abnormality, and this is important because *"there has been some question in some peoples' mind whether this disease might actually be a disease of the mind, and I think finding an abnormality reassures us that this is a genuine physical illness".* The interviewer (Sarah Montague) responded by asking *"Because so many have questioned whether ME even exists?",* to which Professor Belch replied: "*That's absolutely right".* Professor Belch went on to say: *"These children have a terribly damaged lifestyle, and if you add disbelief on to that, the parents don't know whether to believe the child,* (and) *the doctors don't know*". Sarah Montague summarised the findings, saying: "*What you've found is what happens to a body that's reacting to a virus?"*, to which Professor Belch replied:*"That's correct"*, adding: "*There is no doubt that once you have an abnormality to target, treatments can follow"* (http://news.bbc.co.uk/today/hi/today/newsid_8975000/8975412.stm).

Commenting on the Dundee research, Dr Neil Abbot, Director of Operations at MERUK, said: "*The study undoubtedly adds greater scientific weight to the existence of a condition which, sadly, many still fail to acknowledge in spite of its severity"* (http://www.bbc.co.uk/news/uk-scotland-tayside-central-11204884).

The importance of this study cannot be over-emphasised because of the potential long-term consequences for cardiovascular disease and because, as Dr Abbot points out, the white blood cells are releasing an excessive amount of highly reactive free radicals, possibly from exercising muscle (which would contra-indicate incremental aerobic exercise) and the white blood cells provide evidence of *"a persistent or reactivating viral infection triggering apoptosis of white blood cells".*

Many people around the world believe that the Wessely School's "cognitive behavioural model" of ME/CFS (which includes the use of incremental aerobic exercise) has been built on sand, not science. Wessely's own recent comments, together with the now irrefutable evidence of viral involvement in ME/CFS, can only have assisted the cognitive behavioural model's (long overdue) disappearance from the discipline of medicine.

It may be coincidence, but a video is currently circulating on the internet featuring Francis Collins, Director of the NIH, singing “The Times They Are A-Changin’ “ on Capitol Hill (Rock Stars of Science:http://www.youtube.com/watch?v=2SNHDlKYSt0&forumid=331851).

The times are indeed changing for those with ME/CFS because the stranglehold of the Wessely School has finally been severed but they will, naturally, go down fighting because their professional careers in relation to ME/CFS have been shown to be scientifically invalid, a record of which no-one could be proud.