Update on Complaint to the MRC about the PACE Trial in the light of the confirmation of a strong association of a retrovirus with myalgic encephalomyelitis/chronic fatigue syndrome

Margaret Williams **25th August 2010**

It was on 31st March 2010 that a formal complaint about the PACE Trial on ME/CFS was lodged by Professor Malcolm Hooper: a hard copy of "Magical Medicine – How to Make A Disease Disappear" plus a letter were sent by Special Delivery to Dr Morven Roberts, Head of the MRC Clinical Trials Unit. It was received at the MRC and signed for the following day.

There was no acknowledgement, let alone any response, so on 18th June 2010 an enquiry was made by telephone; after a curiously long wait, the enquirer was variously told that (1) Dr Morven Roberts was not Head of the CTU; (2) there was no-one of that name at the MRC; (3) upon asking who *was* Head of the CTU, the enquirer was told it was not the person to whom the enquirer wished to speak and the person answering the telephone refused to provide an alternative name of the Head of a department of a publicly funded body; (4) the enquirer was then told that Dr Roberts *was* Head of the CTU and (4) that Dr Roberts was in a training meeting, and finally the enquirer was told by a plainly panicking young woman: *"I think I'm going to have to put the phone down"*, which she did. The episode was a quite extraordinary response to a simple request to speak to Dr Morven Roberts in relation to a complaint about an MRC study.

The following day Dr Roberts sent Professor Hooper an email:

"Dear Professor Cooper (sic)

I understand that you have recently tried to contact me in regard to your complaint lodged with me as Clinical Trials Manager about the PACE Trial. I can let you know that the MRC are working through the large document you have sent and will respond in due course.

Morven".

Despite it now being over eight weeks since Dr Morven Roberts promised to respond in due course, nothing further has been heard from the MRC about this important complaint.

The results of the PACE Trial are now over-due.

Given that the MRC PACE Trial is a publicly funded study, it is understood that the raw data will eventually have to be disclosed.

In the light of the recently published Lo/Komaroff/Alter et al paper (PNAS 10.1073/pnas.1006901107) that has confirmed and expanded the findings linking a retrovirus to ME/CFS published in Science by Lombardi /Mikovits et al (Science 2009:326:585), namely that there is indeed a strong association between ME/CFS and a family of retroviruses (the same type of virus as HIV/AIDS), the MRC may wish to consider the implications of these two papers in relation to the outcome of the PACE Trial.

The PNAS paper shows that murine leukaemia virus (MLV)-related viral sequences were present in the blood of 86.5% of ME/CFS patients studied and in 6.8% of blood donors acting as controls and that, whilst distinct from XMRV, the *gag* gene sequences identified share 96.6% homology with XMRV (xenotropic murine leukaemia virus-related virus, the retrovirus found by Lombardi/Mikovits et al). Indeed, Dr Harvey Alter, Chief of the Infectious Diseases Division and Associate Director of Research in the Department of Transfusion Medicine at NIH (and winner of the Lasker Award, a most prestigious award in medicine), confirmed in the telebriefing that XMRV is in the same family of retroviruses and that the WPI study is more advanced than his own (not only did the WPI find XMRV, they succeeded in culturing it; they also showed that it could infect other cells and that an immune response had been mounted to it). Whilst the *gag* sequence identified by his team is not XMRV specific, it is a definite marker for the family of murine leukaemia viruses of which XMRV is one, and whilst XMRV is xenotropic (and thus does not infect mice themselves), the type of MLV found by Alter et al is polytropic and thus able to infect both mice and other mammals, including humans. Furthermore, Dr Alter confirmed that, like HIV, these retroviruses are mutating once they are in the body. It is known that even when the virus was undetectable in the blood, it thrived in the reproductive organs as well as the spleen, gut, bladder, lungs, liver and lymph nodes (Qiu, Silverman et al; http://retroconference.org/2010/Abstract/39393.htm). Dr Alter explained in the NIH telebriefing that the current assays are very difficult because the viruses are present in very low titres and require a very sensitive assay. He also stated that his own study "*does at least confirm the findings of the Whittemore Peterson…I think our study is highly confirmatory of their work".*

Notably, Professor Myra McClure from Imperial College, London (a retrovirologist and co-author with psychiatrist Professor Simon Wessely of a UK study that failed to find evidence of a retroviral

association in ME/CFS patients) disagrees with Alter and is on record asserting: "*Let's be clear…They did not confirm (Mikovits') results"* (http://news.sciencemag.org/sciencenow/2010/08/second-paper-supports-viral-link.html). Diplomatically, Dr Alter noted: *"Very good laboratories have come up with different results. And this is not totally explained. We think there are reasons for this. We think it is in the patient populations rather than in the laboratory testing although the latter hasn't been completely ruled out".*

The issue of possible contamination of samples was robustly addressed and dismissed, and of international concern is the implication for the safety of blood transfusions: Australia, Canada and New Zealand have already banned patients with ME/CFS from donating blood and the Japanese Red Cross has confirmed that XMRV has been found in about 2% of Japan's blood supply (http://www.cfscentral.com).

It will be interesting to see how the PACE Trial Principal Investigators interpret their trial data in order to achieve their well-known objective of demonstrating that cognitive restructuring (aka "brain washing") incorporating incremental aerobic exercise successfully disabuses people with ME/CFS of the (entirely correct) notion that they are physically sick, given that it is now indisputable that people with what the PIs assert is the same disorder as that documented in both Science and PNAS is a multi-system neuroimmune disease that has been definitively shown in the cohorts studied to be closely linked to a family of retroviruses (a retrovirus inserts itself into the host's genetic material by copying its genetic code into the DNA of the host by using RNA and once there, it stays for the life of the host).

Despite the PIs' use of the overly-broad Oxford criteria in the PACE Trial, the PIs claim to be studying the same disease as that studied by the WPI and the NIH/FDA/Harvard, a disorder that the PIs continue to assert is a somatoform disorder.

It has not yet been established on what scientific evidence the PIs and other members of the Wessely School

assert that, together with anorexia nervosa, ME/CFS is a "*classical psychosomatic disorder where response to social threat is expressed somatically"* and that "*aberrant emotional processing is a strong candidate as a maintaining factor for these disorders*" (http://www.meactionuk.org.uk/magical-medicine.htm).

It cannot be disputed that the PACE Trial cohort is heterogeneous, given that the Chief PI, Professor Peter White, sought approval from the West Midlands MREC to write to GPs virtually imploring them to send anyone with "*chronic fatigue (or synonym)"* for entry into the PACE Trial, thereby opening the trial to anyone who is simply tired all the time (TATT).

Of considerable concern is the fact that the PACE Trial PIs trained the Trial therapists to convince -- indeed to indoctrinate -- participants that if there really was something wrong with them, it would have been found, as well as urging them not to seek medical help for their symptoms, tactics which many physicians and medical scientists believe are plainly unethical (http://www.meactionuk.org.uk/magical-medicine.htm).

Had the PIs been content to limit their study to those with somatoform disorder instead of insisting that it includes those with ME/CFS on the basis of their unsustainable belief that ME/CFS is a somatoform disorder, there would have been less reason to challenge the PACE Trial. Even so, it would remain open to challenge because the PIs (as well as other influential members of the Wessely School) continue to insist that fibromyalgia and irritable bowel syndrome are, together with ME/CFS, the same single somatoform disorder and they have included such patients in the PACE Trial, even though the evidence continues to mount that neither FM nor IBS is a somatoform disorder any more than is ME/CFS.

See, for example, Hargrove JB et al; Clin EEG Neurosci 2010:41: (3):132-139, a study that found consistent and significant differences in brain function between FM patients and normal controls that supports dysfunctional sensory processing in the spinal cord and brain, as well as abnormal central mechanisms; see also Science News: http://www.sciencedaily.com/releases/2010/08/100819141950.htm, which records that scientists at the Technisches Universitaet Muenchen have demonstrated that micro-inflammation of the gut mucosa causes sensitisation of the enteric nervous system, causing IBS. Using ultrafast optical measuring methods, the researchers were able to demonstrate that mediators from mast cells and enterochromaffin cells directly activate the nerve cells in the bowel. This hypersensitivity of the enteric nervous system upsets communication between the gut's mucosa and its nervous system. Such evidence adds to the plethora of existing evidence that neither FM nor IBS is a somatoform disorder as asserted by Wessely School psychiatrists and it further calls into question the validity of the PACE Trial.

A further related matter in the light of the latest retroviral evidence is the fact that the National Institute for Health and Clinical Excellence (NICE) is due to re-visit its 2007 Guideline on ME/CFS (CG53) in August 2010. CG53 was much criticised for its inappropriate recommendation of only cognitive behavioural interventions for ME/CFS patients. It is interesting to note that one of the NICE Guideline Development Group members, Dr Esther Crawley, a paediatrician who is a strong supporter of the psycho-social model of ME/CFS, has been awarded £164,000 to test the Lightning Process on children with ME/CFS (http://www.bristol.ac.uk/news/2010/6866.html). The Lightning Process is a commercially promoted training programme created by Phil Parker; advertisements for it have been censured for having breached the Advertising Standards Authority regulations by making misleading claims about its efficacy for ME/CFS.

Of note is the fact that the Chief Executive of the charity Action for ME (AfME), Sir Peter Spencer, is a non-executive director of Dr Crawley's employing health authority (The Royal National Hospital for Rheumatic Diseases NHS Foundation Trust) and the charity is fully backing her study. This seems an inconsistent stance by Sir Peter, given that AfME is now calling for the MRC to "*prioritise research into the link between viral infections and ME, following the latest findings from the United States"* (http://www.afme.org.uk/news.asp?newsid=912).

It will be interesting to see how effective the Lightning Process is against retroviruses.

In 1989 Simon Wessely and Trudy Chalder et al wrote: *"One of the principal functions of therapy at this stage is to allow the patient to call a halt without loss of face"* (JRCGP 1989:39:26-29).

As the evidence for retroviral involvement in ME/CFS becomes impossible to dismiss and consequently the Wessely School psycho-social model disintegrates, at what point will Professor Wessely be able to call a halt without loss of face?