

Issues re the use of the Oxford criteria for the MRC "CFS" Trials

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It is noteworthy that in a posting dated 17th June 2004, the ME Association Board of Trustees has spoken out against the MRC PACE and FINE trials on patients with "CFS/ME" in its "Summary of Meeting Held on Tuesday 8 June 2004"; this Summary states: **"A discussion took place on how we are going to pursue our policy of wanting these trials terminated and the money diverted to research aimed at improving our understanding of the underlying physical causes of ME/CFS"**.

Given the unquantifiable magnitude of the "egg-on-the-face" factor if the MRC "CFS/ME" trials were to be terminated, such termination would seem an unachievable goal, so in the meantime the issue of the entry criteria to the MRC trials remains live.

Given that the lead author of the Canadian Consensus Guidelines, Dr B Carruthers, has confirmed that there is no valid reason why the MRC should not use those Guidelines in its studies of ME/CFS, an explanation for the intransigent adherence to the Oxford entry criteria by the MRC trial leaders is still awaited. The most likely reason has been highlighted by Doug Fraser in a cogent post on 19th June 2004 to the eBMJ re: Professor Wessely and Dr White's views, in which Fraser quotes from the Canadian Consensus document itself: **"Care must be taken not to classify patients experiencing chronic fatigue as ME/CFS patients. It is interesting to note that in the treatment review (Whiting et al JAMA 2001:286 (11):1360-1368), all the CBT and GET studies that indicated improvement used the less restrictive Oxford criteria with the exception of the Prins study"**.

Equally, the CDC website is unequivocal: **"Since many illnesses have incapacitating fatigue as a symptom, care must be taken to exclude other known and often treatable conditions before a diagnosis of CFS is made"**.

The point about the Oxford criteria is that they specifically **include** those with other conditions, especially those with psychiatric disorders.

For the record, the CDC website also states about the clinical course that **"Some patients recover completely with time, and some grow progressively worse"**, and in 1996 the CDC recommended the setting up of a brain bank: such a requirement would hardly have been proposed had the CDC been confident that the disorder was amenable to psychotherapy.

The Oxford criteria select patients who **"present with a principal complaint of disabling fatigue of uncertain cause"** and the stated aim of the Oxford meeting **"was to seek agreement amongst research workers for the reporting of future studies of patients with chronic fatigue"**. This is not the case in ME/CFS, where patients experience post-exertional muscle fatigability which is not the same as "fatigue" or chronic tiredness (see JAMA, July 1990).

The Oxford criteria state **"Specifically, we set out to agree on which patients should be included"**: given the stated aim of the Oxford criteria, this means the criteria set out to select patients with chronic fatigue, not ME, yet the MRC study purports to be studying those with "CFS/ME".

The Oxford criteria state: **"The following guidelines were agreed. There are no clinical signs characteristic of the condition. Psychiatric disorders (including depressive illness, anxiety disorders and hyperventilation syndrome) are not necessarily reasons for exclusion"**.

This opens the door to the world and his wife if they feel chronically tired for longer than six months without any medically determined cause; potentially, therefore, those with ME *could* be included in the MRC trial if the trial assessors are not sufficiently exact.

Patients with ME can only be excluded from the MRC CFS trials if those doing the initial assessment *recognise* ME-associated neurological signs (and the classic symptoms) and reject such patients. Given what is known about the aims of the trial leaders, this is unlikely, but if the assessors ignore what patients present to them and therefore permit the inclusion in the MRC CFS trial of those with physical signs (ie. those who might have true ME), then the trial will be flawed by virtue of the fact that the specified Oxford criteria are not being adhered to.

According to Hyde's textbook (The Clinical and Scientific Basis of ME CFS; ed BM Hyde, J Goldstein & P Levine, The Nightingale Research Foundation, Ottawa, 1992), the physical signs (as distinct from symptoms) seen in ME come under the following headings: vital signs; cutaneous; ophthalmological; neurological; genito-urinary; muscular; gastroenteric and orthopaedic.

In "Postviral Fatigue Syndrome" edited by Rachel Jenkins and James Mowbray (John Wiley & Sons, Chichester, 1991), Rachel Jenkins (currently Director of the WHO Collaborating Centre at The Institute of Psychiatry that produced the now notorious "Guide to Mental Health in Primary Care" which included ME/CFS as a mental disorder in defiance of the WHO ICD-10 classification of it as a neurological disorder) quotes Goodwin, who in 1981 argued in the Lancet that it was important that the title "myalgic encephalomyelitis" should be restricted to patients who show some of each of the three major features of the disease: firstly, signs and symptoms in relation to muscles, such as recurrent episodes of profound weakness, fatiguability and marked muscle tenderness; secondly, neurological signs and symptoms such as pyramidal or cranial nerve lesions, especially affecting the eyes, or weakness of peripheral muscles, as documented by the voluntary muscle test, or involvement of the autonomic nervous system (demonstrated by orthostatic tachycardia, abnormal coldness of the extremities, episodes of sweating, episodes of pallor, bladder and bowel disturbance) and thirdly, biochemical abnormalities.

Taken together with the history, the presenting symptomatology and the overall clinical picture, ME/CFS is not difficult to diagnose, as Professor Jenkins herself stated in the British Medical Bulletin as long ago as 1991: **"Once one is familiar with the concept of post-viral fatigue syndrome, such patients are in practice not too difficult to differentiate from those with true psychiatric illnesses such as depressive illnesses, anxiety, hypochondriasis or hysteria. In addition, specific cognitive abnormalities are present in ME, including difficulty in marshalling material, difficulty in finding the correct words in a sentence, and in appropriate syntax; speech is somewhat slurred, and the patient appears more clumsy than usual. They tend to bump into doorways and furniture more frequently, may display old bruises, and may complain of a feeling of dysequilibrium. The physical symptoms should be an aid to diagnosis, although they may be wrongly attributed to primary psychological illness unless care is taken in eliciting them. Under a regime of pushing beyond physical limits, severe relapses occur and physical limits decrease. People with this illness do not tolerate antidepressants well. Patients are often very scared and in considerable pain"**.

(Assessment and Diagnosis of ME in the Psychiatric Clinic. Rachel Jenkins. In: Postviral Fatigue Syndrome pp241-246. British Medical Bulletin 1991:47:4: Ed: PO Behan, DP Goldberg and JF Mowbray).

Since the issue of the Oxford entry criteria for the MRC CFS trials is of cardinal importance to such a significant percentage of the population, those who bear responsibility for the trials may wish to consider the following.

PHYSICAL SIGNS that may be present in and are characteristic of ME (all are documented in the ME/CFS literature) include the following (not in any particular order, and it is important to recognise the variability of such signs in the same patient, which itself is characteristic of ME; it is also important to be aware that not all patients have all signs):

a typically swinging low-grade temperature that tracks a definite pattern that is absolutely classic of Ramsay-described ME (how often do psychiatrists look at temperature charts?)

- observable sweats and shivers
- thermodyregulation
- inability to walk any distance
- sluggish visual accommodation
- conjunctival injection
- palprebal swelling (usually left side)
- excessive drying of tear and buccal glands
- unequal and contrary pupillar reactions
- irregular pupil movement
- nystagmus that is variable and jelly like: it might be present at 9am; not present at 1pm; present at 3pm, not present at 7pm and present at 10pm. The fact that a single, cursory look does not find it to be present does not mean that it is not present
- positive Romberg (absolutely typical of true ME, but not of chronic fatigue)
- abnormal tandem stance
- abnormal gait
- abnormality of vestibular function
- coarse hand tremor
- fine-finger incoordination

- diaphragmatic incoordination
- shortness of breath on minimal exertion (those with ME show significant reduction in all lung function parameters)
- incoordination of larynx and oesophagus (resulting in the need to swallow carefully to avoid choking)
- cogwheel movement of the leg on testing
- muscle bunching / spasm
- fasciculation
- carpopedal spasm
- blepharospasm
- hyper-reflexia without clonus
- loss of abdominal reflexes
- neck and back stiffness
- bronchial hyper-responsiveness
- sometimes profound muscle weakness with inability to sustain muscle strength (for example, patients may not be able to sustain enough strength to pump up a sphygmomanometer cuff --- they start off without difficulty but cannot continue)
- irregular, bounding pulse
- increase in pulse rate after minimal activity
- nocturnal bradycardia
- recurrent palpitations
- orthostatic tachycardia
- typically labile B/P
- demonstrable neurally-mediated hypotension
- flattened or even inverted T-waves on 24hr monitoring (not usually apparent on a standard 12 lead ECG but there nevertheless if looked for)
- cyanotic nail beds
- vasculoid rash
- specific, clearly-defined vascular demarcation that can cross dermatomes

- blotchy, discoloured hands and feet
- marked coldness of the extremities
- mottled malar erythematous discolouration similar to that seen in lupus
- one-sided palpable oedematous swelling of face (usually left sided)
- marked facial pallor
- secondary Raynaud's signs (acute changes are visible)
- recurrent, severe mouth ulcers
- red pharyngeal crescents
- non-androgenous hair loss
- destruction of fingerprints (atrophy of fingerprints due to perilymphocytic vasculitis and vacuolisation of fibroblasts)
- palpable lymph glands (not exceeding 2 cm --- if so, look for another cause)
- may be enlarged liver and spleen
- disturbed bladder and bowel function

Unless looked for, such signs as there are in ME/CFS can easily be missed.

Bearing in mind the requirement for compliance with the Oxford criteria, on what precise grounds can the MRC "CFS/ME" trials that will rely on the Oxford criteria for entry into the trials include those with ME, who may have an abundance of characteristic physical signs?