Science or Psychology?

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"Wessely School" psychiatrists and supporters, and indeed all proponents of the current Medical Research Council PACE trials, including the new Government-funded Centres for those with "CFS/ME", not forgetting the NHS, the Department of Health and its various Ministers and of course, the Benefits Agency and the medical insurance industry, might wish to consider two recent – and opposing – views about exercise in ME/ICD-CFS (ie. in ICD-classified G93.3 ME/ICD-CFS and not, it must be emphasised, in other non-specific states of chronic fatigue).

In an article entitled "The Placebo Response in the Treatment of Chronic Fatigue Syndrome: A Systematic Review and Meta-Analysis" by Simon Wessely and a team from King's College, London, Section of General Hospital Psychiatry (published in Psychosomatic Medicine 2005 March-April:67(2):301-313), the authors studied 29 other studies (note, not actual patients) and found that only 14% of patients responded well to psychiatric interventions as many "CFS" sufferers "have a firm conviction that their illness is of physical origin".

On 22nd March 2005 The Washington Post reported on this study: "Researchers say people need to be convinced that behavioural therapy and regular exercise can help them overcome symptoms of chronic fatigue syndrome. **Researchers said that patients should be made aware that behavioural therapy and regular exercise can alleviate their symptoms".**

By contrast, an impressive and significant study of actual patients **found that exercise exacerbates the symptoms that define (ME) / CFS** (Exercise responsive genes measured in peripheral blood of women with Chronic Fatigue Syndrome and matched control subjects by Toni Whistler, James F Jones, Elizabeth R Unger and Suzanne D Vernon from the Viral Exanthems and Herpesvirus Branch of the CDC at Atlanta: BMC Physiology 2005:5:5).

[Note: **Complement** is an immune system process by which the action of antibodies against the antigen --- the invading agent --- is completed. **Gene ontology** describes how gene products behave in a cellular context. It is not a database of gene sequences nor a catalogue of gene products].

"While physiologic disturbance in acute illness is transient, chronic illnesses such as CFS have prolonged disturbances. **Activities that are physiologic stressors, such as physical exercise, exacerbate the symptoms that define (ME)CFS**".

"We used gene expression profiling of peripheral blood to evaluate differences between (ME)CFS subjects and sedentary controls both before and following an exercise challenge. **Of importance, most differences were present prior to exercise challenge".**

"These differences were in G-protein-coupled receptor and ion transport and ion channel activity ontologies. These differences may help explain the symptoms of (ME)CFS".

"21 genes were identified as being differentially expressed. Among the 21 genes, 16 could be categorized in the Gene Ontology (GO) of biological processes and 15 in molecular function. The most significant categories pertained to the biological process of transport (both vesicle-mediated and protein transport)".

"Exercise-related changes that were seen only in (ME)CFS subjects (and not in controls) were related to G-protein-coupled receptor signalling".

"Gene ontology comparison was used to evaluate differences between control and (ME)CFS subjects before (baseline) and after exercise. Baseline differences that continued after exercise involved GO terms relating to ion transport. **After exercise, these difference appear to be amplified".**

"Interestingly, complement activation was one of the exercise induced differences between subjects and controls that was present only after challenge".

The authors draw specific attention to Wessely's previously published findings (Clinical improvement in chronic fatigue syndrome is not associated with lymphocyte subsets of function or activation: Clin Immunol Immunopathol 1997:82:83-91) in specific terms: "**Because this difference in gene expression is so dramatic, it implicates a fundamental peturbation in the biochemical activity of lymphocyte and monocyte peripheral blood fractions from (ME)CFS subjects compared with controls that does not affect classical immunologic markers (ie. CD45) that have been shown to be unaffected in (ME)CFS patients. Rather, low expression of these genes may have subtle effects on immune function".**

"Gene expression profiling affords a unique opportunity to characterize (ME)CFS at a systems biology level. In a (previous) study, we found that (ME)CFS patients had different mononuclear cell gene expression pattern than non-fatigued controls. In addition, differential display polymerase chain reaction on a small number of (ME)CFS patients and control subjects identified candidate biomarkers in the peripheral blood".

"Class comparison was used to identify these 21 differentially expressed genes, which indicated the possible disturbance of biologic pathways. We used the GO comparison that is based on the knowledge that gene expression levels are dependent variables in biologic processes, cellular components, and molecular functions**.** The GO categories considered significantly different when comparing (ME)CFS subjects with controls were those pertaining to ion transporter activity (a total of 87 genes applied to this category in the comparison of (ME)CFS and controls after exercise) and ATPase activity coupled to transmembrane movement (42 genes). When the (ME)CFS and control classes are compared prior to exercise, ion transport activity and voltage-gated, ion channel activity are identified".

"It is evident that ion transport and ion channel activity segregate cases from controls and that exercise seems to intensify these differences".

"Several other conditions have been reported in which fluctuating fatigue occurs that are known to be caused by abnormal ion channels. These conditions include multiple sclerosis and polyneuropathies".

"There are other transmembrane functions associated with differences between controls and (ME)CFS patients, including signal transducer activity (which) occurs by a number of mechanisms. The G-protein-coupled receptors play an important role in the membrane trafficking machinery. The most obvious exercise-induced changes in (ME)CFS cases pertain to gene regulation at the point of chromatin structure (and for the chromatin architecture category, the (ME)CFS comparison highlighted 7 overlapping ontologies containing 59 unique genes, compared with 1 ontology of 33 genes in the control comparison)".

"One interesting correlate of this study was the finding that the complement pathway showed significant differences between (ME)CFS and control subjects after exercise. This has been reported previously by Sorensen at al (J Clin Immunol 2003:112:397-403). **Complement activation was identified as an ontology that was significantly different between (ME)CFS and control subjects after exercise".**

"Class discovery tools will also be applied to (ME)CFS subjects' expression profiles in an attempt to further describe discrete subsets of this disease on the basis of gene expression, as these analytical tools will prove to be very helpful in defining the pathophysiology of (ME)CFS. It is hoped that this encompassing approach to (ME)CFS research will open many doors to the understanding of this syndrome".

One can but wonder if the Medical Directors of the UK's two adult patient-based charities (as distinct from research-based charities that do not have members, such as MERGE), namely the ME Association and Action for ME, have immediately brought this important research to the urgent attention of both the MRC and the Directors of the new Government-funded Centres that are set to deliver compulsory exercise regimes throughout the NHS to hapless ME/ICD-CFS patients.

It is to be hoped that the Medical Directors also notify the company that now runs the UK Benefits Agency because in October 2004 the ME Association magazine ME Essential reported Government proposals that would force those with ME/ICD-CFS who claim Incapacity Benefit to have a medical check-up every three months and to undergo (quote) "continuous reassessment".

Why does the UK ME/ICD-CFS community have to rely on Dr Derek Enlander from the US to write to Prime Minister Blair and inform him that: "Over the past several years there is a tragedy in the manner in which the NHS and British politicians treat ME/CFS. Under your watch, millions of pounds have been misspent supporting ill-founded psychiatric notions of this disease. The cognitive behavioural programme that your government has funded is inherently flawed, in fact does harm. There is NO evidence of treatment efficacy in behaviour modification or paced therapy in this disease. It is time for a government White Paper on (ME)CFS, addressing methods of diagnosis and treatment and rational multi-discipline research. I was your predecessor's Physician-in Waiting on his New York trips. I look forward to meeting you on your next New York visit". It is to be hoped that they do indeed meet.