Vilified but Vindicated?

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NOTE: ***Myalgic Encephalomyelitis (ME) is also known as Chronic Fatigue Syndrome (CFS) in the International Classification (ICD-10; G93.3) and in order to differentiate this disorder from what the psychiatrists call "CFS/ME", for the avoidance of doubt we refer to it as "ME/ICD-CFS".***

ME/ICD-CFS sufferers have for many years been unjustly subjected to assertions that they suffer not from an organic condition but from either depression or from somatisation disorder, both of these being primary psychiatric disorders. Such assertions have been promulgated mainly by adherents of the "Wessely School", so-named after its main protagonist Professor Simon Wessely from Guy's, King's and St Thomas' School of Medicine and The Institute of Psychiatry in London.

However, a newly published 30 page review by Professor Leonard Jason et al from DePaul University, Chicago, exposes the lack of evidence for such assertions and makes it imperative that the currently advocated management regime propounded by Wessely et al that is supported by the Medical Research Council (MRC) and funded by Government be held to rigorous scrutiny, since this regime avoids the cardinal issues surrounding ME/ICD-CFS and leaves many very sick people with no hope of correct treatment or support.

The review in question is entitled "Chronic Fatigue Syndrome: The Need for Subtypes" and is published in Neuropsychology Review: 2005:15:1:29-58.

It contains factual evidence which extinguishes, as unsustainable assumption, Wessely's theory that is currently driving all UK NHS provision for those with ME/ICD-CFS, namely, that disorders such as ME, fibromyalgia, multiple chemical sensitivity and irritable bowel syndrome are "somatisation" (which in his lecture at The Royal Society of Medicine on 29th October 1999 he defined as "the most common expression of emotional distress in the world"). Wessely and his co-authors believe that such syndromes are but one unified psychiatric disorder which they name a "Functional Somatic Syndrome", referring to the different syndromes as being "like the elephant to a blind man – simply different parts of a larger animal" and claiming that "the existence of specific somatic syndromes is largely an artefact of medical specialisation" (see "Functional somatic syndromes: one or many?" Lancet:1999:354:936-939).

The total inadequacy of the psychiatric approach has been repeatedly pointed out to the Chief Medical Officer (CMO) and to the MRC by us and by others: indeed, during the life of both the CMO's "independent" Working Group and the MRC's Research Advisory Group (RAG) we submitted substantial published evidence that addressed the urgent need for the investigation of sub-groups of "CFS/ME" but the evidence was comprehensively and systematically ignored. Indeed, not only were our submissions ignored, but for our opposition to the dominant psychiatric lobby and for doing no more than drawing attention to the available published evidence, we were

subjected to a sustained campaign of abuse backed up by threatening letters from solicitors.

Because the issue of subgrouping is cardinal to the advancement of understanding of the disorder and because the evidence remains valid, before quoting from Jason et al's latest review we briefly summarise here one of our submissions to both the CMO's Working Group and to the MRC RAG in which we addressed the need for sub-groups. The extract below was compiled in response to a Restricted Policy document dated 2nd December 2000 written personally by Professor Anthony Pinching (when Deputy Chair of the CMO's Working Group) in which he advised the Working Group that sub-grouping of "CFS/ME" was unnecessary, stating: ***"It seems appropriate to regard CFS/ME as a single clinical entity…(the question of sub-groups) may be considered a matter of semantics and personal philosophy…".*** Not only was the available evidence disregarded, but Pinching's document was published as Annex 4 to the CMO's Working Group Report ("General concepts and philosophy of disease") and this Report remains to date the definitive position of UK Government bodies.

In our submission we stated: "There is now an unmistakable recognition that sound research has strengthened the need for consideration of subgroups" and we provided the following evidence:

1. A Subgroup Analysis of Cognitive Behavioural Treatment Studies. Fred Friedberg. *JCFS 1999:5:3-4:149-159*

2. Estimating rates of chronic fatigue syndrome from a community-based sample: a pilot study. Jason LA et al. *Am J Community Psychol 1995:23(4):557-568;*

3. Politics, Science and the Emergence of a New Disease. The case of Chronic Fatigue Syndrome. Jason LA et al. *Am Psychol 1997:52:9:973-983*

4. Chronic fatigue syndrome, Fibromyalgia and Multiple Chemical Sensitivities in a community-based sample of chronic fatigue syndrome - like symptoms. Jason LA et al. *Psychsom Med 2000:62(5):655-663*

5. Brain MRI abnormalities exist in a subset of patients with chronic fatigue syndrome. John DeLuca, Benjamin H Natelson et al. *J Neurol Sciences 1999:171:3-7*

6. Fatigue 2000 Conference Proceedings. The National ME Centre in conjunction with The Essex Neurosciences Unit. 23-25 April 1999

7. Severe and very severe patients with chronic fatigue syndrome: perceived outcome following an inpatient programme. DL Cox LJ Findley. *JCFS 2000:7(3):33-47*

8. Symptom patterns in long-duration chronic fatigue syndrome. Fred Friedberg et al. J *Psychsom Res 2000:48:59-68*

A recent Editorial in the Journal of Chronic Fatigue Syndrome (Editoral: Roberto Patarca-Montero. JCFS 2000:7(4):1) makes the point that "the sorting of patients into subpopulations….is helping in the design and interpretation of clinical trials for therapeutic interventions aimed at particular disease manifestations".

The authors of the 1994 CDC criteria for CFS themselves recommend that researchers use stratification techniques to identify subgroups of patients (The Chronic Fatigue Syndrome: A Comprehensive Approach to its Definition and Study. Keiji Fukuda, Michael C Sharpe et al. *Ann Int Med 1994:121:12:953-9)*

One clear message which emerged from the National Institutes of Health (NIH) State of the Science Conference on CFS held on 23-24 October 2000 in Arlington, Virginia was that CFS is heterogeneous and researchers ***must*** subgroup patients by features including chronicity, immunology and neuroendocrinology (Conference calls for Serious Research. T.Lupton. *CFIDS Chronicle 2001:14:1:12-13).* Conference participants included Dr David Bell, Professor Dedra Buchwald and Professor Nancy Klimas, all world-renowned experts on CFS.

Roberto Patarca-Montero, Assistant Professor of Medicine and Director of the Laboratory of Clinical Immunology, University of Miami School of Medicine (and Editor of The Journal of Chronic Fatigue Syndrome) emphasises the importance of subsets of patients in his paper "Directions in Immunotherapy" (Directions in Immunotherapy. Roberto Patarca-Montero. *The CFS Research Review 2001:2:1).*

Experienced researchers and clinicians presented evidence at the Fifth International AACFS Conference held in Seattle, 27-29 January 2001 about the need for subgrouping. Some examples include the following:

--- Professor Leonard Jason from De Paul University, Chicago, concluded that "Subtype differences detected may account for some of the inconsistencies in findings across prior studies that have grouped CFS patients into one category. Subtyping patients according to more homogeneous groups may result in more consistent findings which can then be used to more appropriately and sensitively treat the wide range of illness experience reported by different types of individuals with CFS"

--- Professor Kenny de Meirleir from Brussels compared immunological profiles in three different subgroups of CFS patients; he found significant differences between the groups

--- Dr Pascale de Becker from Brussels presented evidence that there is a need to assess the homogeneity of a large CFS population in order to establish those symptoms which can improve differentiation of CFS patients

--- Dr Paul Levine from Washington demonstrated that factor analysis is an important tool for separating subgroups of CFS; he showed that it should be utilised in future attempts to develop case definitions for CFS to identify discrete patient groups, which may have different pathogeneses and responses to treatment

--- Dr Katherine Rowe from Australia presented evidence showing that at least three distinct subgroups can be identified within the CFS syndrome

--- A large international multicentre study of autoimmunity was presented by E.Tan (with, amongst others, participants from The Scripps Research Institute, La Jolla,

California; the University of Washington; Harvard Medical School, Boston; State University of New York and George Washington University,Washington DC. Of interest is that another participant was Simon Wessely from Kings College, London). This large study reflected the heterogeneity from one CFS centre to another; it emphasised the importance of subcategorising CFS studies".

In our submission, we drew specific attention to a discussion document produced for the CMO's Working Group by Dr Derek Pheby of The Unit of Applied Epidemiology, Frenchay Campus, Bristol, who said: **"If progress is to be made, it is necessary to consider…the possible existence of subgroups within the population of patients with CFS / ME.** The increasing knowledge of pathological processes occurring in CFS / ME has led to a belief that it should be possible to define subgroups on the basis of biomarkers and thus to draw a distinction between CFS and ME. **It has been argued by many that not only can ME be differentiated from CFS by biological markers, but that its clinical features also differ".** Under "Priority Areas for Research", Pheby concluded: "Certain areas for research have been identified as being important in enabling the Working Group to achieve its objectives. These include…systematic reviews to consider **subgroups**". Like our own submissions, this document disappeared without trace.

Let us hope that the new paper by Jason et al does not suffer a similar fate because it cannot be too highly recommended: all members of the ME/ICD-CFS community are urged to obtain a copy for themselves and to promote it extensively because by its extensive review of the need for subgrouping, it vindicates the ME community's repeatedly ignored calls for action that will address their suffering.

Since the Jason et al paper is 30 pages long and represents quite a challenging read for those with ME/ICD-CFS, the following extracts are provided:

"Individuals with CFS have been found to differ (depending upon) the case definition utilized. As a result of this heterogeneity, findings emerging from studies are, at best, discrepant, and at worst, contradictory. Heterogeneity among participant groups can also contribute to a lack of observable abnormalities in some laboratory studies. One of the greatest sources of diagnostic unreliability is criterion variance (ie.) differences in the formal inclusion and exclusion criteria used by clinicians to classify patients into diagnostic categories (and) these different definitions pose difficulties in interpreting results of studies….(comparing differences in the existing criteria), Jason et al (2002c) found a symptom currently not part of the Fukuda criteria, shortness of breath, (which) did differentiate the groups. Recently, a new clinical case definition for ME/CFS has been developed in Canada (in which) postextertional malaise must occur with loss of physical or mental stamina. A cluster analysis was performed to define a typology of chronic fatigue symptomatology (Jason and Taylor, 2002); one key characteristic that contained almost all participants with CFS was markedly high severity of postexertional fatigue. Results from this investigation highlight the importance of this symptom as a diagnostic marker for CFS".

"It is important to decide whether or not syndromes such as CFS, fibromyalgia (FM) and irritable bowel syndrome (IBS) are best understood in terms of a unitary model of functional somatic distress or as separate diagnostic entities. As an example of this type of research, Sullivan et al (2002) used latent class analysis with 32 symptoms of

patients with CFS, FM and CFS, and FM and the findings supported the notion that CFS and FM have more similarities than differences. However, these investigators deliberately removed the major criteria symptoms for both syndromes before conducting the analyses. In contrast, a study by Taylor et al (2001b) evaluated the diagnostic validity of conditions that have been labelled functional somatic syndromes. Results supported diagnostic distinctions between five syndromes (FM, CFS, somatic depression, somatic anxiety, and IBS)".

"In an influential review article, David (and Wessely) et al (1991) concluded that depression occurs in about 50% of CFS cases, while somatisation disorders occur in about 25% of cases. These findings have led some to conclude that CFS is solely a psychiatric disorder. Clauw and Chrousos (1997) argue that the inability of science to identify the precise physiologic basis for CFS should not lead to labelling an individual with CFS as having a psychiatric disorder".

"The Diagnostic Interview Schedule (DIS), a structured psychiatric instrument, has frequently been used to assess psychiatric comorbidity in CFS samples. However, this instrument was not designed for use with medically ill populations. By contrast, the Structured Clinical Interview for the DSM-IV (SCID) uses all potential sources of information (and its use) is limited to highly trained clinicians more able to recognize the subtle distinctions between CFS and psychiatric disorders".

"The Fukuda et al (1994) criteria do not exclude people who have purely psychosocial or psychiatric reasons for their fatigue (and) this broadening of the CFS definition raises questions regarding the extent to which patients with purely psychiatric explanations are erroneously included within the CFS rubric".

"Is it possible that some patients with a primary affective disorder could be misdiagnosed as having CFS? Some CFS investigators would not see this as a problem because they believe that high rates of psychiatric comorbidity indicate that CFS is mainly a psychiatric disorder and that distinctions between the two are superficial and merely a matter of nomenclature".

"The erroneous inclusion of people with primary psychiatric conditions in CFS samples will have detrimental consequences for the interpretation of both epidemiologic and treatment efficacy findings".

"It is important to subclassify: some medical illnesses (e.g. multiple sclerosis, hyperthyroidism) have been shown to elicit psychological disorders; changes in mood, fatigue and malaise are commonly associated with infection (Ray 1991) and depression and anxiety are common in patients with cancer and heart disease. Ray (1991) noted that depression that accompanies a prolonged illness may be better conceptualised as demoralization rather than as psychiatric illness, particularly in ambiguous illnesses in which patients have difficulty gaining recognition of the legitimacy of their illness".

"Lange et al (1999) found no MRI differences between those with CFS and healthy controls. However, when the CFS group was divided into those with and without a psychiatric disorder occurring since their CFS diagnosis, 66.7% of those without psychiatric comorbidity had MRI abnormalities. The CFS group without psychiatric

diagnosis had the highest frequency of MRI small, punctate, subcortical white matter hyperintensities. Even though it is unclear what the functional consequences are of having more lesions among CFS patients without psychiatric diagnoses, subtyping those with and without psychiatric comorbidity seems warranted".

Jason et al then present substantial evidence, divided into sections, to support their call for subgrouping of "CFS".

The section dealing with neurocognitive dysfunction concludes: " Subtyping on whether or not patients have deficits on specific tasks (e.g. reaction times, motor processing, performance on complex attentional and memory tests) might help resolve conflicting studies in this area".

In the section on "Community versus Tertiary Care Recruitment", Jason et al note that Wessely et al (1997) determined that 2.6% of the sample had CFS according to the Fukuda et al (1994) criteria and note: "It is of interest that these rates are within the range of prevalence of several mood disorders (and) are considerably higher than those reported in other CFS epidemiological studies. Wessely did indicate that the 2.6% rate of CFS included both those with and without a psychiatric diagnosis, and if only those without a psychiatric diagnosis were counted, the CFS rate would be only 0.5%".

In the section on "Sociodemographic, Psychosocial and Illness Subtypes", Jason et al note: "When grouping individuals diagnosed with CFS as a heterogeneous whole, it is possible that abnormalities typical of a specific group are not seen….the fact that significant findings from one study are frequently not replicated is a strong indicator that each sample contains a different mix of subtypes of CFS, making replication nearly impossible". They note that "Levine (1997) found that individuals with sudden onset have a better prognosis than those with gradual onset" and that "the presence of a stressful life event preceding onset of CFS is another factor that may differentiate subgroups of patients with CFS (Ray et al, 1995; Salit, 1997; Theorell et al, 1999).
Jason et al point out that Pheley et al (1999) found that while recovery from CFS was rare, those patients who had less severe illness initially were more likely to have a positive prognosis.

The authors note that "Patients diagnosed with both CFS and FM have been found to be substantially more disabled than patients with either condition alone (Bombadier and Buchwald, 1996)" and that "Jason et al (2000d) found in a community sample of CFS that 15.6% also had FM, 40.6% had Multiple Chemical Sensitivities (MCS) and 3.1% had FM and MCS", and conclude that "Future studies should subclassify patients according to whether they are pure types or have FM and/or MCS".

The section entitled "Medical Subgroups" considers the promising evidence that has been obtained by studying subtypes under headings that include virology, immunology, neuroendocrinology, autonomic, neurologic and genetic areas, noting that: "There has been a lack of consistency in CFS laboratory findings, which may be a function of combining distinctive groups of patients into a large heterogeneous group rather than analysing them within subtypes (as) within CFS there does appear to be mounting evidence of brain and immune system abnormalities (Komaroff

2000a). Several researchers have suggested that there might be biomarkers that can differentiate patients with CFS into different subtypes".

In the section on Virology, Jason et al note: "Lane et al (2003) found that muscle biopsy samples from 20.8% of the CFS patients were positive for enterovirus sequences, but all the controls were negative. Nine of the ten enterovirus positive cases were among those with abnormal lactate response to exercise".

In the Immunology section, Jason et al remind readers that Landay et al (1991) were the first group to identify that activation markers CD38 and HLA-DR were increased and that the suppressor cell population (CD8 CD11b) was reduced in CFS, which suggested that decreased suppressor cells might lead to a hyperimmune response. "People with CFS appear to have two basic problems with immune function: a) poor cellular function, with low natural killer cell cytotoxicity and frequent immunoglobulin deficiencies (most often IgG1 and IgG3) and b) elevations of activated T lymphocytes, including cytotoxic T cells, and elevations of circulating cytokines. Natelson et al (2005) recently found increases in cytokines (which) supports the hypothesis that in some patients with CFS, symptoms may be due to immune dysfunction within the central nervous system".

Also in the Immunology section, Jason et al draw attention to the fact that another biologically-based marker involves the 2'-5'A antiviral pathway, which causes the production of RNase-L (a pathway in all cells that can be activated by viral infections or toxins), with activation resulting in destruction of messenger RNA, stating: "This is a desperate action taken by cells to prevent the proliferation of viruses (and) it interferes with the ability of the cell to make its own protein. Patients with CFS have higher elevations of RNase-L than patients with any other disease".

On the RNase-L issue, Jason et al are categoric: "Enough evidence does exist to recommend subtyping on this dimension", advice that is in stark contrast to that of Dr Charles Shepherd (Medical Adviser to the ME Association and member of the CMO's Key Group) who, when we suggested to the CMO's Working Group that the RNase-L issue merited attention, wrote personally on 17th July 2001 – and with the intention of discrediting us -- to the CMO that: "I acknowledge that I have opposed the inclusion of testing for RNase L activity. One of the major problems is that all the published information so far comes from researchers who have a financial interest in their promotion – a situation which involves a clear conflict of interest", a serious allegation by Shepherd which appeared to cast doubt on the integrity of leading researchers, including those of professorial status in America and Belgium.

The section on Immunology notes that: "Borish et al (1998) found evidence of low level inflammation, similar to that of allergies, in a subgroup of individuals with CFS. Borish suggested that there might be two subgroups, those with immune activation (infectious or inflammatory) and those devoid of immune activation. Natelson et al (1993) found that those with on-going inflammatory processes reported greater cognitive disabilities. Buchwald et al (1997) found individuals with CFS to have significant abnormalities in C-reactive protein (an indicator of acute inflammation) and neopterin (an indicator of immune system activation) when compared to controls and stated that groups of individuals with active low-level inflammatory, infectious processes could be identified and that this was evidence of

an organic process. Cook et al (2001) found that individuals with an abnormal MRI and on-going inflammatory processes scored significantly worse on measures of physical disability".

"When elevated, eosinophil counts can indicate the presence of allergic inflammation. Several studies have reported significant elevations of eosinophil counts in individuals with CFS. Elevated levels of lymphocytes can be indications of conditions such as viral infection, chronic infection and Hodgkin's disease (and) elevated lymphocytes have also been reported for CFS samples (Patarca 2001)".

"A positive ANA (antinuclear antibodies) test can indicate the presence of inflammatory disease. Elevated rates of ANA have been reported with CFS samples (Nesher et al, 2001)".

Jason et al conclude the section on the need for subgrouping of ME/ICD-CFS patients on immunological grounds by noting: "Routine blood tests might provide useful information for subtyping patients with CFS into infectious, inflammatory and "other" categories".

In the section of neuroendocrinology, Jason et al point out that "Scott and Dinan (1999) described patients with CFS as having reduced adrenal secretory reserve and their adrenal glands are smaller compared to healthy subjects, whereas in major depression, enlarged adrenal glands are found. It is possible that some patients with CFS have a cortisol deficiency and others do not, but when all patients are combined into one large CFS category, these important differences are ignored".

In the same section, the authors note: "Endicott (1999) has found that patients with CFS have parents with increased prevalence of cancer and autoimmune disorders when compared to control patients' families". The authors observe that: "Symptom heterogeneity may be due to different axes of the stress response and therefore efforts are needed to better develop ways to subgroup on this dimension, as some individuals might be in an early and others in a later phase of the illness process".

Also in this section, Jason et al draw attention to the mechanisms of a shift from a Th1 to a Th2 immune response, noting the work of Van Konynenburg (2003b): "the HPA axis and sympathetic nervous system become upregulated. These raise the secretion of glucocorticoids and catecholamines (adrenalin and noradrenalin), which cause a Th1 to Th2 immune response shift. Because of the shift to Th2, the body does not have an effective defence against viral or intracellular bacterial infections (and) the immune system tries to respond but it cannot do so effectively because of the suppression of the immune system by the HPA axis and the sympathetic nervous system. Later, the HPA axis becomes downregulated but there is still not an effective Th1 response to attack the viral infection, however, now the immune system may cause inflammation (explaining the ANA levels). The patient with CFS now has ineffective protection from viruses and intracellular bacteria or from inflammation".

At this point in the review, Jason et al draw attention to the work of Cleare (2004), a member of the CMO's Working Group Key Group and close colleague and co-author with Wessely and who, like many of the Wessely School psychiatrists, also works for

the medical insurance industry: “Cleare suggests that the neuroendocrine changes are in response to physical deconditioning”.

In the section on the autonomic nervous system, Jason et al note heart rate variability analysis and observe that: “Controls evidenced increases in the intensity of sympathetic transmission to the heart, whereas patients showed a decrease in the intensity (which was) even more pronounced for the patients with CFS**. These findings suggest that the sympathetic system might be exhausted in patients and might be incapable of responding to a stressful challenge”.**

In the same section, Jason et al point out: “Natelson’s group recently found that in response to postural stress, 81% of patients and none of controls experienced ejection fraction decreases (suggesting left ventricular dysfunction in the heart**), with the resulting low flow circulatory state possibly making it difficult for patients to meet the demands of everyday activity** (Peckerman 2003b). Streeten and Bell (2000) found the majority of patients with CFS had striking decreases in circulating blood volume (and) it appears that the blood vessels in patients with CFS are constricted dramatically but efforts to restore normal volume have met with limited success. In addition, Yoshiuchi et al (2004) have found that patients with CFS have lower cerebral blood flow than sedentary controls, and neither psychiatric illness nor illness severity plays a role in this reduced brain blood flow”.

The section concludes: “Subtyping individuals with CFS for these types of cardiac and blood circulation problems seems warranted”.

In the neurology section, Jason et al discuss existing evidence of MRI abnormalities and spinal fluid abnormalities and state: “Subgrouping patients into those with normal and abnormal MRI or spinal fluid would be recommended for investigators that have access to these types of tests”. The section also considers how immunogenic stimuli can alter brain circuitry, changing its sensitivity to unrelated subsequent stimuli and the section concludes: “Rather than searching for cytokine irregularities in patients with CFS, an alternative approach might involve subtyping those with and without heightened central nervous system sensitivity to stimuli such as cytokines”.

The genetics section discusses existing work on gene expression profiling as a means of subgrouping those with CFS, noting that differentially expressed genes in CFS patients were associated with immune functioning.

In a section looking at pharmacological and non-pharmacological interventions, Jason et al make the crucial observation that “If there are distinct subgroups, as has been suggested in this article, then treatments need to be tailored to the differential needs of patients with CFS”.

In considering pharmacological interventions, the authors state: “Regardless of the medication, it is important to note that very few pharmacological agents have been well-established as effective”, whilst on the issue of non-pharmacological interventions (ie. cognitive behavioural therapy), they note that although CBT “has been described as one of the more promising treatment approaches (Whiting et al, 2001), its application to CFS has been controversial”, and note that in a critique of the

Prins et al study (2001), Van Hoof (2004) maintains that 28% did not complete the CBT study and that the effects of CBT were no longer present after three years.

In relation to CBT, Jason et al point out that: "Because the findings of the British studies have been widely disseminated, it is not uncommon for medical practitioners to encourage patients with CFS to begin an exercise programme and to challenge their beliefs about the medical aetiology of their disorder. Typical of the purely psychogenic explanations for CFS is a research group from the Netherlands (Vercoulen et al, 1998), who believe that individuals with CFS attribute their symptoms to physical causes, are overly pre-occupied by their physical limitations, and do not maintain regular activity. When Song and Jason (in press) tested this model, it fitted only with the chronic fatigue participants who had psychiatric reasons for their fatigue. The fact that this model could not be replicated with either the CFS group or those with medical reasons for their chronic fatigue suggests that CFS and chronic fatigue due to psychiatric causes are not the same condition".

"Several studies do suggest that subgroups of patients with CFS do react differently to exercise than healthy controls: Sorensen et al (2003) found that patients with CFS evidence increases in complement protein C4a at six hours after an exercise challenge. This single protein (C4a) could be a diagnostic marker for CFS after an exercise challenge. Peckerman et al (2003) suggested that there might be left ventricular dysfunction in the heart of some CFS patients, **and lower cardiac output could make it difficult for patients to exercise.** For some individuals with low cortisol levels, activity such as exercise that increases the stress hormones could lead to a further drop in cortisol levels (and) exercise could subsequently lead to postexercise adrenal insufficiency (which) could be responsible for the severe postexertional fatigue that patients with CFS experience. **Bruno (2004) recommends that those with CFS not engage in exercise or activities that further stress metabolically damaged, overworked neurons.** As with evidence in the CFS literature, Bruno states that deconditioning rarely occurs".

Concluding this section, Jason et al note the need to understand the different needs of subtypes of patients with CFS, stating that: "tailored interventions are needed for the unique needs of different subgroups of patients. Understanding how non-pharmacological interventions (ie. CBT and graded exercise) differentially affect patient subgroups might provide insights into the pathophysiology of this illness".

In the Discussion section, Jason et al state: "CFS represents a heterogeneous syndrome and the lack of consistency in studies might very well be a failure to routinely classify CFS cases into subtypes. Currently, there is a need for investigators to develop subtypes and ultimately improve sensitivity (ie. ability to identify those who have the subtype) and specificity (ie. ability to correctly define those who do not have the subtype). Routine collection of a standard set of variables might provide investigators with large pooled data sets to explore some of the more promising subtypes".

"The current US case definition for CFS (Fukuda et al 1994) is characterised by vaguely worded criteria that lack operational definitions (and) some samples have included a high or low percentage of patients with critical CFS symptoms (eg. postexertional malaise). The Canadian case definition does include these critical

symptoms and use of such types of case definition might aid in the selection of more homogeneous samples".

"It is clear that the current cohort of individuals diagnosed with CFS is a diverse group with varying disease course and disability patterns, offering limited understanding of the aetiology or pathology of the illness. Patterns of illness course and duration are difficult to decipher when using the current diagnostic criteria".

"The current method of grouping all individuals who meet diagnostic criteria together is complicating the identification of biological markers of the subgroups. When diagnostic categories lack reliability and accuracy, the quality of treatment and clinical research of such populations can be significantly compromised. Most importantly, if there are many distinct subtypes within a diagnostic category, samples will not be similar, as they will have different percentages of critical characteristics, symptoms, and biomarkers**. A misdiagnosis may lead to improper treatment and in cases of severe illness, the matter of an incorrect diagnosis can have serious consequences. If there is limited reliability of the diagnostic groups studied, because of the failure to attend to subtype differences, the results of any study using such diagnostic categories are likely to be unreliable or invalid".**

"There is some risk that samples of individuals with chronic fatigue and somatic symptoms include those with (i) solely psychiatric diagnoses, (ii) solely CFS diagnoses, and (iii) CFS and psychiatric comorbidity. Therefore, these three groups need to be differentiated and analysed separately as opposed to being collapsed into one category**. If inappropriate use of a case definition leads to the inclusion of individuals who have a purely psychiatric condition, this heterogeneity of patients with CFS and psychiatric conditions will present difficulties in interpreting the results of epidemiologic and treatment studies".**

It seems to us that there could be no more powerful or timely warning, especially given that the MRC PACE trials intend to use the Oxford 1991 criteria, which are even more inclusive of psychiatric disorders than the Fukuda 1994 criteria.

The ever-mounting evidence of serious organic pathology in ME/ICD-CFS will soon be impossible to brush aside, even by the well-organised and well-funded psychiatric lobby which so suits Government, the pharmaceutical industry and medical insurance interests; indeed, as the latest paper by Jason et al shows, it is no longer credible for adherents of the "Wessely School" to remain in denial.

However, persistently uninfluenced by scientific evidence and because their unauthorised attempt to reclassify ME/ICD-CFS as a mental disorder in the WHO Guide to Mental Health in Primary Care was eventually thwarted by the UK ME community, these influential psychiatrists and their paymasters are currently endeavouring to convince the compilers of the next DSM revision (DSM-V: the mental health "bible" which takes precedence over ICD classifications) to include a new category of "functional somatic syndromes" into which "CFS" would be placed and would thereby become an officially classified mental illness.

It has been said that for democracy to work, an intelligent electorate is essential. Similarly, we would suggest that for ME activism to work, an informed and

committed community is essential. It must surely be inescapable to most people in the UK ME community that it is singularly ill-advised to rely on either of the major adult ME charities to over-turn the status quo of psychiatric domination. Although we can, and do, supply the tools, it is up to individual members of the ME community to make effective use of those tools by insisting on dynamic action by Members of Parliament. We understand that one large ME support group in the UK actively denies its members knowledge of our articles. We submit that the deliberate suppression of publicly available information is not democracy but dictatorship and that such dictatorship can best be overcome by papers such as this latest one from Jason et al, to whom immeasurable gratitude is due.