

Comments on the PACE debate held in House of Lords (Grand Committee) on 6th February 2013

The Countess of Mar's question was to ask HMG "what assessment they have made of the effects of the PACE trial on provision of health and social care and welfare benefits for people with CFS/ME" so one would have expected that this would have been the focus of the debate.

Apart the Countess of Mar, there were six speakers before the acting Minister (Baroness Northover, a Government Whip, and a last minute stand-in for the Minister, Lord Howe, Parliamentary Under Secretary of State at the Department of Health) attempted to address Lady Mar's question.

From watching the debate live on the web and from reading it in Hansard, it is difficult not to conclude that the six speakers were part of an orchestrated response to promote the PACE trial as a magnificent piece of scientific research and as a vehicle of support for Professor Sir Simon Wessely, whose claims of "vilification" by CFS/ME patients were once again afforded a public platform.

It is understood that Wessely was instrumental in the speeches and that Professor Lord Turnberg (who was present but who did not speak) had briefed all the doctors. Lord Turnberg, known for his support of Wessely, was President of The Royal College of Physicians at the time the 1996 Joint Royal Colleges' report on CFS (CR54) was published; he later denied knowledge of the many complaints about it that were sent to him at the RCP and to some of which he had personally replied, claiming that the report was well-received. It recommended that no investigations should be performed on CFS/ME patients to confirm the diagnosis.

Despite their recent public denials, their published articles confirm that Wessely and Professor Peter White (Chief Principal Investigator of the PACE trial) regard CFS/ME as a psychiatric disorder and this was reflected by the speakers who followed the Countess of Mar: Wessely's published record can be summed up in one sentence: *"I will argue that ME is simply a belief, the belief that one has an illness called ME"*, whilst White's view is contained in his contribution to the standard medical textbook (Clinical Medicine, edited by Kumar and Clark) in which CFS/ME is listed under "Functional or Psychosomatic Disorders: Medically Unexplained Symptoms", which White asserts were previously known as: *"'all in the mind', imaginary and malingering"*. For this, Peter White got an OBE for his services to medical education on CFS/ME.

At times, the debate turned into a paen of praise for Wessely and White, rather than a factual discussion of the effects of the PACE trial on the people it was supposed to help. As the Medical Advisor to the ME Association, Dr Charles Shepherd, commented on 8th February 2013 on an internet forum:

"I was at the House of Lords on Wednesday evening for the debate. Sadly, I thought it was a very disappointing debate because after the Countess of Mar had made her speech, everyone else basically just read out prepared speeches which gave uncritical support to all aspects of the PACE trial....I don't think anyone managed to deal with some of the difficult questions that were being asked – mainly because the answers weren't in their scripts".

The speakers were, in order:

Lord Robert Winston (Labour), a gynaecologist renowned for his work on human fertility and his television programmes about it;

Lord John Alderdice (Liberal Democrat), a former part-time psychiatrist engaged in Northern Irish politics;

Baroness Molly Meacher (Cross Bencher), ex-wife of Labour MP Michael Meacher and now wife of Lord Layard; a social worker who worked for the Mental Health Foundation and who since 2004 has been Chair of the East London and City Mental Health Trust, for which the PACE Chief Principal Investigator also works and whom she greatly respects; in 1974 she published her report "Scrounging on the Welfare";

Lord Richard Layard (Labour), current husband of Baroness Meacher and an economist concerned with reducing unemployment; he became known as the “Happiness Tsar” because of his promotion of cognitive behavioural therapy (CBT), which he said would get “unhappy” people back to work – in 2005 he presented his paper “Mental Health: Britain’s Biggest Social Problem?” to the No.10 Strategy Unit and advocated for an extra 10,000 therapists to deliver CBT across the nation in 250 new treatment centres, which were to include children (Will this man make you happy? Stuart Jeffries: The Guardian, 24th June 2008);

Baroness Sheila Hollins (Cross Bencher), professor of the psychiatry of learning disability at St George’s, University of London and a past President of the Royal College of Psychiatrists and

Baroness Margaret Wheeler (Labour), former member of the Enquiry Panel into productivity and high performance, Department of Trade and Industry and also of Investors in People Advisory Board, Committee for Employment and Skills.

None of the above speakers was qualified to speak on the effects of the PACE trial on people with CFS/ME and all spoke outwith their own area of expertise.

Whilst not medically qualified, Lady Mar has many years’ experience of close involvement with the subject and is familiar with the facts. Her speech was meticulously researched and supported by sound references. She spoke truthfully, knowledgeably and genuinely.

Three possibilities need to be considered: that, with the exception of the Minister, (i) the other speakers were ignorant about the subject under discussion, in which case why were they speaking in a public debate?; (ii) they were incompetent, which would explain why they presented misinformation and (iii) there was an orchestrated and calculated intention to proclaim the success of the PACE trial by friends and supporters of the psychiatrists involved with it.

For those who have long been aware of the politics and the medical insurance issues surrounding CFS/ME, the correct answer is not difficult to deduce.

1. Lord Winston

Lord Winston was not present at the start of the debate and missed the first part of Lady Mar’s speech.

He said, authoritatively, about the persistent fatigue in CFS/ME: *“It is not relieved by rest, which is and has been puzzling for a long time”*. Lord Winston is apparently unaware of the extensive peer-reviewed biomedical literature which has demonstrated pathological abnormalities after exercise and at rest in CFS/ME subjects that explains the muscle fatigue, for example:

In **1984**, Arnold et al demonstrated excessive intracellular acidosis of skeletal muscle on exercise in ME/CFS patients, with a significant abnormality in oxidative muscle metabolism and a resultant acceleration in glycolysis (Proceedings of the Third Annual Meeting of the Society for Magnetic Resonance in Medicine, New York: 1984: 12-13).

In **1985**, UK researchers demonstrated muscle abnormalities in ME/CFS patients: *“The most important findings were type II fibre predominance, subtle and scattered fibre necrosis and bizarre tubular structures and mitochondrial abnormalities. About 75% of the patients had definitely abnormal single fibre electromyography results”* (Goran A Jamal Stig Hansen JNNP 1985:48:691-694).

In **1987**, Leonard Archer demonstrated that: ***“Relapses are precipitated by undue physical or mental stress. However compelling the evidence for an hysterical basis may be, there is further, equally***

compelling, evidence of organic disease. Some patients do have frank neurological signs. **Muscle biopsies showed necrosis and type II fibre predominance**" (JRCGP: 1987:37:212-216).

In 1988 there was "general agreement that (ME's) distinguishing characteristic is severe muscle fatigability, **made worse by exercise. It becomes apparent that any kind of muscle exercise can cause patients to be almost incapacitated (and) the patient is usually confined to bed. What is certain is that it becomes plain that this is an organic illness in which muscle metabolism is severely affected**" (Crit Rev Neurobiol: 1988:4:2:157-178).

Also in 1988, UK researchers Archard and Bowles et al published the results of their research into muscle abnormalities in ME/CFS: **"These data show that enterovirus RNA is present in skeletal muscle of some patients with postviral fatigue syndrome up to 20 years after onset of disease and suggest that persistent viral infection has an aetiological role. These results provide further evidence that Coxsackie B virus plays a major role in ME, either directly or by triggering immunological responses which result in abnormal muscle metabolism"** (JRSN 1988:81:325-331).

Again in 1988, Teahon et al published a study of skeletal muscle function in ME/CFS; it showed significantly lower levels of intracellular RNA, suggesting that ME/CFS patients have **an impaired capacity to synthesise muscle protein, a finding which cannot be explained by disuse** (Clinical Science 1988: 75: Suppl 18:45).

In 1989, Professor Tim Peters spoke at a meeting of microbiologists held at the University of Cambridge: **"Other muscle abnormalities have been reported, with decreased levels inside the cell of a key enzyme called succinate dehydrogenase, which plays an important role in energy production inside the mitochondria (the power house of the cell)"**. A report of this conference was published in the ME Association Newsletter, Autumn 1989, page 16.

In 1990, the BMJ published an important study: **"Patients with the chronic fatigue syndrome have reduced aerobic work capacity compared with normal subjects. We found that patients with the chronic fatigue syndrome have a lower exercise tolerance than normal subjects. Previous studies have shown biochemical and structural abnormalities of muscle in patients with the chronic fatigue syndrome"** (Aerobic work capacity in patients with chronic fatigue syndrome. MS Riley DR McClusky et al BMJ:1990:301:953-956).

In 1991, evidence of muscle damage in ME/CFS was demonstrated by Professor Wilhelmina Behan from Glasgow: **"The pleomorphism of the mitochondria in the patients' muscle biopsies was in clear contrast to the findings in the normal control biopsies. Diffuse or focal atrophy of type II fibres has been reported, and this does indicate muscle damage and not just muscle disuse"**. This study was done on a homogeneous population and 80% of the biopsies showed structural damage to the mitochondria (Acta Neuropathol 1991:83:61-65).

In 1992, US researchers (including Robert Gallo, the co-discoverer of the HIV virus) found that **"57% of patients were bed-ridden, shut in or unable to work. Immunologic (lymphocyte phenotyping) studies revealed a significantly increased CD4 / CD8 ratio. Magnetic resonance scans of the brain showed punctate, subcortical areas of high signal intensity consistent with oedema or demyelination in 78% of patients. Neurologic symptoms, MRI findings, and lymphocyte phenotyping studies suggest that the patients may have been experiencing a chronic, immunologically-mediated inflammatory process of the central nervous system"** (Dedra Buchwald, Paul Cheney, Robert Gallo, Anthony L Komaroff et al Ann Intern Med 1992:116:2:103-113).

Also in 1992, the US Department of Health and Human Services produced a pamphlet on ME/CFS for the guidance of physicians (NIH Publication No. 92-484) which stated: **"ME/CFS symptoms overlap with those of many well-recognised illnesses, for example, lupus erythematosus (SLE) and multiple sclerosis. Psychiatric evaluations fail to identify any psychiatric disorders. Many people with ME/CFS have neurologic symptoms, including paraesthesiae, dysequilibrium and visual blurring. Evidence suggests that several latent viruses may be actively replicating more often in (ME)CFS patients than in healthy control subjects. Most investigators believe that reactivation of these viruses is probably**

secondary to some immunologic challenge. It is important to avoid situations that are physically stressful”.

In 1993, Professor Anthony Komaroff from Harvard published his “Clinical presentation of chronic fatigue syndrome” in which he stated: ***“ME/CFS can last for years and is associated with marked impairment. (It) is a terribly destructive illness. The tenacity and ferocity of the fatigue can be extraordinary. As for the symptoms that accompany the fatigue, it is striking that these symptoms are experienced not just occasionally but are present virtually all the time. In our experience, 80% of patients with ME/CFS have an exceptional post-exertional malaise. (Physical examination findings) include abnormal Romberg test (and) hepatomegaly (and) splenomegaly. Anyone who has cared for patients with ME/CFS will recognize that (the) description of the patient with lupus eloquently describes many patients with ME/CFS as well”*** (In: Chronic Fatigue Syndrome. John Wiley & Sons, Chichester. Ciba Foundation Symposium 173:43-61).

In 1993, UK researchers Barnes et al **demonstrated that there is a significant abnormality in oxidative muscle metabolism with a resultant acceleration in glycolysis in ME/CFS patients** [*cf. the work of Arnold in 1984 above*] (JNNP:1993:56:679-683).

In 1995, UK researchers Lane and Archard published their article “Exercise response and psychiatric disorder in chronic fatigue syndrome”, which stated: ***“In previous studies patients with ME/CFS showed exercise intolerance in incremental exercise tests. We examined venous blood lactate responses to exercise at a work rate below the anaerobic threshold in relation to psychiatric disorder. Our results suggest that some patients with ME/CFS have impaired muscle metabolism that is not readily explained by physical inactivity or psychiatric disorder”*** (BMJ 1995:311:544-545).

That same year (1995), UK researchers Geoffrey Clements et al reported that: ***“Enteroviral sequences were found in significantly more ME/CFS patients than in the two comparison groups....This study provides evidence for the involvement of enteroviruses in just under half of the patients presenting with ME/CFS and it confirms and extends previous studies using muscle biopsies. We provide evidence for the presence of viral sequences in serum in over 40% of ME/CFS patients”*** (J Med Virol 1995:45:156-161).

In 1996, Pizzigallo E et al reported: ***“We performed histochemical and quantitative analysis of enzymatic activities and studies of mitochondrial DNA deletions. All specimens showed hypotrophy, fibres fragmentation, red ragged fibres, and fatty and fibrous degeneration. Electron microscopy confirmed these alterations, showing degenerative changes, and allowed us to detect poly/pleomorphism and cristae thickening of the mitochondria. The histochemical and quantitative determination of the enzymatic activity showed important reduction, in particular of the cytochrome-oxidase and citrate-synthetase. The ‘common deletion’ of 4977 bp of the mitochondrial DNA was increased as high as 3,000 times the normal values in three patients. Our results agree with those of Behan et al 1991 and Gow et al 1994. The alterations are compatible with a myopathy of probable mitochondrial origin (which) could explain the drop in functional capability of the muscle”*** (JCFS 1996:2:(2/3):76-77)

In 1998, UK researchers Russell Lane and Leonard Archard published their findings of muscle abnormalities in response to exercise in ME/CFS patients: ***“The object of this study was to examine the proportions of types I and II muscle fibres and the degree of muscle fibre atrophy and hypertrophy in patients with ME/CFS in relation to lactate responses to exercise, and to determine to what extent any abnormalities found might be due to inactivity. Muscle fibre histometry in patients with ME/CFS did not show changes expected as a result of inactivity. The authors note...an inflammatory infiltrate, and it would seem that inflammation and class I MHC expression may occur in biopsies from patients with ME/CFS. The authors note that this is of some interest, as they have argued previously that some forms of ME/CFS may follow a previous virally-mediated inflammatory myopathy”***. In general, following exercise, patients with ME/CFS showed more type I muscle fibre predominance and

infrequent muscle fibre atrophy, unlike that which would be expected in healthy sedentary people. (JNNP 1998:64:362-367).

In 1999, Paul et al provided irrefutable evidence of delayed muscle recovery after exercise. That paper states: ***“The use of 31 P-nuclear magnetic resonance (31 P-NMR) has now provided positive evidence of defective oxidative capacity in ME/CFS. Patients with ME/CFS reach exhaustion more rapidly than normal subjects, in keeping with an abnormality in oxidative metabolism and a resultant acceleration of glycolysis in the working skeletal muscles. When the rate of resynthesis of phosphocreatine (PCr) following exercise is measured, this abnormality is confirmed. (This) provides a conclusive demonstration that recovery is significantly delayed in patients with ME/CFS. The results demonstrate that patients with ME/CFS fail to recover properly from fatiguing exercise and that this failure is more pronounced 24 hours after exercise”*** (European Journal of Neurology 1999:6:63-69).

In 2000, a Belgian/Australian collaborative study entitled “Exercise Capacity in Chronic Fatigue Syndrome” was unequivocal: ***“Comparing the exercise capacity in our patients with data from other studies shows a functionality similar to that of individuals with chronic heart failure, patients with chronic obstructive pulmonary disease, and those with skeletal muscle disorder”***. Specific findings included (i) the resting heart rate of patients was higher than controls but patients’ maximal heart rate at exhaustion was lower than controls (ii) the maximal workload achieved by patients was almost half that achieved by controls (iii) the maximal oxygen uptake was almost half that achieved by controls. This would affect patients’ physical abilities, leading the authors to comment: ***“This study clearly shows that patients with ME/CFS are limited in their capabilities”***. Taken together, these findings ***“suggest that alteration in cardiac function is a primary factor associated with the reduction in exercise capacity in ME/CFS”*** (P De Becker et al. Arch Intern Med 2000:160:3270-3277).

In 2001 an Australian study by Sargent, Scroop, Burnett et al from the Adelaide CFS Research Unit found that ME/CFS patients are not de-conditioned and that ***“There is no physiological basis for recommending graded exercise programmes”*** (The Alison Hunter Memorial Foundation ME/CFS Clinical and Scientific Meeting, Sydney, Australia, December 2001). This was later published (Med. Sci. Sports Exerc: 2002:34:1:51-56) and the authors stated: ***“The fatigue is often present at rest and exacerbated by the simplest of physical tasks. The purpose of the present study was to employ ‘gold standard’ maximal exercise testing methodology. Exercise performance is well recognised to be impaired in ME/CFS patients, with a reduced exercise time to exhaustion being a common finding. The present findings indicate that physical deconditioning (is not) a critical factor in the fatigue that (patients) experience. Although the recommendation or imposition of exercise-training programmes may have benefit in terms of social interaction, such programmes could well be based on a false premise if the intention is to improve well-being by correcting the effects of deconditioning”***.

In 2003, Professor Ben Natelson from the US found that ***“The patients with ME/CFS (indicated) profound physical impairment. These scores tended to be below the published norm for patients with cancer, congestive heart failure and myocardial infarction”*** (J Nerv Ment Dis 2003:191:324-331).

In 2003 a UK study of skeletal muscle tissue by neurologist Russell Lane et al provided evidence of impaired mitochondrial structure and function in ME/CFS patients, once again demolishing the “de-conditioning” theory (JNNP: 2003:74:1382-1386).

In the Summer of 2004, Professors Christopher Snell and Mark VanNess from the University of the Pacific (specialists in muscle function who have been involved in ME/CFS research since 1998) published an article in The CFIDS Chronicle in which they wrote: ***“Healthcare professionals often recommend aerobic exercise as a cure-all for the symptoms of ME/CFS without fully understanding the consequences (and) the results can be devastating (and can lead to) symptom exacerbation, post-exertional malaise and even collapse. It is obvious that persons with ME/CFS do not recover well from aerobic activity. This may be because, for them, the activity is not aerobic. The aerobic system depends on a constant supply of oxygen being delivered to active muscles. There is evidence that this***

*process may be impaired in ME/CFS. In the absence of an adequate supply of oxygen, energy production shifts to anaerobic (without oxygen) process, leading to oxygen debt. Oxygen debt equals fatigue and before normalcy can return (that debt) must be repaid. Interest rates on the (oxygen debt) may be significantly high. **Exercise therapy for ME/CFS will not work because one size does not fit all**".*

In October **2004**, at the 7th AACFS International Conference held in Madison, Wisconsin, Susan Levine from Columbia presented evidence of an analysis of metabolic features using MRSI (magnetic resonance spectroscopy imaging) which showed elevated lactate levels in ME/CFS patients, suggesting mitochondrial metabolic dysfunction similar to mitochondrial encephalomyopathy. Elevation of thalamic choline was also demonstrated, suggesting the presence of neuronal damage.

At the same International Conference, Spanish researchers (Garcia-Quintana) presented their work on aerobic exercise, providing evidence of low maximal oxygen uptake in ME/CFS patients. This confirmed previous studies showing that patients with ME/CFS have a markedly reduced aerobic work capacity on bicycle ergometry.

At this Conference, findings were presented by a Belgian team (Nijs) which provided **evidence of underlying lung damage through intracellular immune dysregulation, with impairment of cardiopulmonary function** – elevated elastase levels could damage lung tissue and impair oxygen diffusion across the alveoli in the lungs, **potentially explaining decreased oxygen delivery to tissues, including muscles, that is seen in ME/CFS**. (This presentation was singled out as being outstanding).

In **2005**, Black and McCully published their results of an exercise study in patients with ME/CFS: *"This analysis suggests that ME/CFS patients may develop **exercise intolerance** as demonstrated by reduced total activity after 4 – 10 days. The inability to sustain target levels, associated with pronounced worsening of symptomatology, suggests the subjects with ME/CFS had reached their activity limit"* (Dyn Med 2005: Oct 24: 4 (1): 10).

Black and McCully's results concur with those of Bazelmans et al that were published in the same year. That study examined the effects of exercise on symptoms and activity in ME/CFS: *"**For ME/CFS patients, daily observed fatigue was increased up to two days after the exercise test. For controls, fatigue returned to baseline after two hours. Fatigue in ME/CFS patients increased after exercise**"* (J Psychosom Res 2005:59:4:201-208).

Also in **2005**, Jammes et al assessed increased oxidative stress and altered muscle excitability in response to incremental exercise in ME/CFS patients: *"The data reported here were taken from well-rested subjects and **research has demonstrated that incremental exercise challenge potentiates a prolonged and accentuated oxidant stress that might well account for post-exercise symptoms in ME/CFS**"* (J Intern Med 2005: 257 (3):299-310).

In **2006**, Belgian researchers Nijs and De Meirleir reported on the observed associations between musculoskeletal pain severity and disability, noting that pain was as important as fatigue to ME/CFS patients: *"Research data gathered around the world enables clinicians to understand, at least in part, musculoskeletal pain in ME/CFS patients...Infection triggers the release of the pro-inflammatory cytokine interleukin-1 β which is known to play a major role in inducing cyclooxygenase-2 (COX-2) and prostaglandin E2 expression in the central nervous system. Upregulation of COX-2 and prostaglandin E2 sensitises peripheral nerve terminals. Even peripheral infections activate spinal cord glia (both microglia and astrocytes), which in turn enhance the pain response by releasing nitric oxide (NO) and pro-inflammatory cytokines. **These communication pathways can explain the wide variety of physiological symptoms seen in ME/CFS. Experimental evidence has shown that ME/CFS patients respond to incremental exercise with a lengthened and accentuated oxidative stress response, explaining muscle pain and post-exertional malaise as typically seen in ME/CFS.** In many of the published studies, graded exercise therapy has been adopted as a component of the CBT programme (i.e. graded exercise was used as a way to diminish avoidance behaviour towards physical activity). **Unfortunately, the studies examining the effectiveness of GET/CBT in ME/CFS did not use musculoskeletal pain as an outcome measure (and) none of the studies applied the current***

diagnostic criteria for ME/CFS. From a large treatment audit amongst British ME/CFS patients, it was concluded that approximately 50% stated that GET worsened their condition. Finally, graded exercise therapy does not comply with our current understanding of ME/CFS exercise physiology. Evidence is now available showing increased oxidative stress in response to (sub)maximal exercise and subsequent increased fatigue and post-exertional malaise (Manual Therapy 2006: Aug. 11(3):187-189).

In **2007**, collaborating researchers in Japan and America noted that people with ME/CFS reported substantial symptom worsening after exercise, symptoms being most severe on the fifth day. **There was no cognitive or psychological benefit to the exercise, and patients suffered physical decline** (Yoshiuchi K, Cook DB, Natelson BH et al. Physiol Behav July 24, 2007).

Also in **2007**, Klimas et al reported: *"Gene microarray data have led to better understanding of pathogenesis. Research has evaluated genetic signatures (and) described biologic subgroups. Genomic studies demonstrate abnormalities of mitochondrial function"* (Curr Rheumatol Rep 2007;9(6):482-487).

In **2007** Nestadt P et al reported neurobiological differences in (ME)CFS: *"These results show that a significant proportion of patients diagnosed with (ME)CFS have elevated ventricular lactate levels, suggesting anaerobic energy conversion in the brain and/or mitochondrial dysfunction"*. Elevated blood lactate levels after mild exercise are considered to be a sign of mitochondrial damage (IACFS International Research Conference, Florida).

In **2008**, a collaborative study involving researchers from Belgium, the UK and Australia (published by J Nijs, L Paul and K Wallman as a Special Report in J Rehabil Med 2008;40:241-247) examined the controversy about exercise for patients with ME/CFS. *"ME/CFS describes a disorder of chronic debilitating fatigue that cannot be explained by any known medical or psychological condition. The Cochrane Collaboration advises practitioners to implement graded exercise therapy for patients with ME/CFS, using cognitive behavioural principles....This approach to GET advises patients to continue exercising at the same level even when they develop symptoms in response to exercise (citing Fulcher KY and White PD, BMJ 1997;314:1647-1652)....Conversely, there is evidence of immune dysfunction in ME/CFS, and research shows further deregulation of the immune system in response to too-vigorous exercise, leading to an increase in fatigue and post-exertional malaise. It has been shown that even a 30% increase in activity frequently triggers a relapse...The severe exacerbation of symptoms following exercise, as seen in patients with ME/CFS, is not present in other disorders where fatigue is a predominant symptom. This post-exertional malaise is a primary characteristic evident in up to 95% of people with ME/CFS. It is possible that exercise at ANY intensity that exceeds an ME/CFS patient's physical capabilities may result in the worsening of symptoms. Early approaches to GET advised patients to continue exercising at the same level when they developed symptoms in response to the exercise. This led to exacerbation of symptoms and adverse feedback from patients and patient charities"*.

In **2008** a paper by Professor Julia Newton et al (Hollingsworth JG, Newton JL et al; Clin Gastroenterol Hepatol 2008;6(9):1041-1048) compared mitochondrial function in patients with primary biliary cirrhosis (PBC), patients with primary sclerosing cholangitis, patients with ME/CFS and normal controls. To define mitochondrial function in peripheral muscle during exercise, (31)P magnetic resonance spectroscopy was used. The authors state about ME/CFS patients: *"Interestingly, prolonged time to maximum proton efflux was also seen in the (ME)CFS control group, indicating that there are aspects of muscle pH handling that are abnormal in this important clinical group"*.

Professor Newton is Lead Clinician in the internationally renowned Cardiovascular Investigations Unit at the University of Newcastle, UK. In her Conference pack for the ME Research UK International Research Conference held at the University of Cambridge on 6th May 2008, Professor Newton said: *"Recent results from a series of MR scans have shown impaired proton removal from muscle during*

exercise in patients with ME/CFS compared to matched controls. This has led us to hypothesise that fatigue arises due to impaired pH run off from muscle during exercise which is influenced by the degree of autonomic dysfunction”.

In 2009, Light et al published evidence demonstrating that after moderate exercise, CFS/ME patients show enhanced gene expression for receptors detecting muscle metabolites and that these were highly correlated with symptoms of both physical and mental fatigue and pain. **The marked alterations in gene expression from circulating leucocytes of CFS/ME patients after exercise suggest that such alterations could be used as objective biomarkers, with ~ 90% of the CFS/ME patients being distinguishable from controls using four of the genes measured** (The Journal of Pain 2009: doi:10.1016/j.pain.2009.06.003).

In 2009, a team led by Professor Myra Nimmo (an internationally renowned metabolic physiologist from the Strathclyde Institute of Pharmacy and Biomedical Sciences in Glasgow) found that during an incremental exercise test, **the power output at the lactate threshold was 28% lower in ME/CFS patients than in matched controls and in addition, F2-isoprostanes (indicators of oxidative stress) were higher in patients than in controls at rest, as well as after exercise and after 24 hours.** These results confirm the earlier work of Kennedy et al from Dundee which showed raised levels of isoprostanes in ME/CFS patients at rest. **Not only do Nimmo’s results show that the levels remain high during exercise and in the recovery period, but that the level of isoprostanes in “rested” ME/CFS patients was as great as that reached by the healthy controls after exercise** (Scandinavian Journal of Medicine and Science in Sports 2009: doi:10.1111/j.1600-0838.2009.00895.x).

In 2009, Pietrangelo T and Fulle S et al published a transcription profile analysis of the vastus lateralis muscle in male and female (ME)CFS patients. They used global transcriptome analysis to identify genes that were differently expressed in the vastus lateralis, and their results are significant. **They found that the expression of genes that play key roles in mitochondrial function and oxidative balance (including superoxide dismutase) were altered in (ME)CFS patients. Other genes that were altered in these patients include the genes involved in energy production, muscular trophism and fibre phenotype determination. Importantly, the expression of a gene encoding a component of the nicotinic cholinergic receptor binding site was reduced, suggesting impaired neuromuscular transmission.** The authors argue that these major biological processes could be involved in and/or responsible for the muscle symptoms of (ME)CFS (Int J Immunopathol Pharmacol 2009;22(3):795-807).

Despite the irrefutable evidence of mitochondrial dysfunction and damage in patients with ME/CFS, the NICE Guideline on “CFS/ME” proscribes mitochondrial testing and recommends only behavioural modification in the form of cognitive behavioural therapy, together with incremental aerobic exercise, and refers to **“perceived exertion”** (52 page version, page 30). It claims that it **“offers the best practice advice on the care of people with CFS/ME”** (52 page version, page 6) and that its advice is **“evidence-based”**. Citing Professor Peter White, the Guideline Development Group specifically stated: **“If patients complained of increased fatigue, they were advised to continue at the same level of exercise”** -- Fulcher and White, BMJ 1997;314:1647-1652). **Given the evidence of mitochondrial damage, such advice cannot conceivably qualify as “best practice advice”.**

On what evidence did Lord Winston advise their Lordships that the existence of persistent fatigue in CFS/ME remains “puzzling”?

Reading from his script, Lord Winston referred to his search of Medline that produced 5,874 papers on CFS/ME which, he said, showed that **“extensive work”** had been carried out on the condition. This misses the point: the 5,874 entries include letters and comments and in fact only 394 of these entries are classed as clinical trials. It is only when comparisons are made between the number of papers on CFS/ME with, for example, multiple sclerosis, that it can be seen how under-researched CFS/ME is. The prevalence of MS is about half that of CFS/ME, yet there are only one tenth the number of clinical trials in CFS/ME than for MS. This means that approximately 20 times more research is conducted into MS than into CFS/ME, so, proportionately, there has not been “extensive” research into CFS/ME at all (MEDLINE total research entries on 8th February 2013 show 55,251 for MS but only 5,883 for

CFS/ME, whilst for MS there are 3,014 clinical trials as opposed to 394 for CFS/ME). Hence, Lord Winston misled their Lordships.

He also said he had made a list of papers published in the last year but he named people known to be strong supporters of the psychiatrists' psychosocial model of CFS/ME. What he failed to tell their Lordships was that in the last year, there were almost six times as many papers published on the biomedical underpinnings of CFS/ME than on the psychosocial model.

Although he also mentioned Professor Julia Newton from Newcastle, he did not mention that her work has demonstrated in CFS/ME patients dysfunction of the autonomic nervous system, abnormal heart rate, abnormal blood pressure regulation, impaired cardiovascular responses to standing, markedly reduced cardiac mass and substantially slower recovery of skeletal muscle from standard exercise.

Lord Winston therefore further misled their Lordships and the Minister when he said *"Effectively, they all come to the same conclusions; namely that at the present time, the best treatment is almost certainly along the lines of cognitive behavioural therapy"*.

He certainly misled their Lordships when he stated that *"what is different about the PACE study is that it is a detailed, controlled study which has extremely rigorous entry into it"*. The PACE study was not a controlled study. Although the PACE trial literature refers to it as an RCT (randomised controlled trial) and although funding and ethical approval were granted on that basis, the PIs decided it would be impractical for it to be a controlled trial so they dropped that element. Lord Winston should have seen that the publication in The Lancet referred to it only as "a randomised trial" (Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial).

Contrary to Lord Winston's statement, the PACE trial did not require *"extremely rigorous entry" criteria*: on the Chief PI's own written admission, it used wide entry criteria (the psychiatrists' own Oxford criteria): *"We chose these broad criteria in order to enhance generalisability and recruitment"* (Trial Identifier, section 3.6). Deliberately to broaden entry criteria for a clinical trial to include patients with general "fatigue" who do not have the disorder in question (CFS/ME) contravenes elementary rules of scientific procedure. The Oxford criteria were described at the time by one of the co-authors:

"British investigators have put forward an alternative, less strict, operational definition which is essentially chronic (6 months or more) ...fatigue in the absence of neurological signs, (with) psychiatric symptoms...as common associated features" (A.S. David; BMB 1991;47:4:966-988). That is not a definition of ME, for a diagnosis of which there must always be neurological signs and the defining feature of ME, namely post-exertional exhaustion and malaise, without which a diagnosis of ME cannot be made.

In 1995 Professor White himself stated: *"The Oxford criteria are more widely defined...(and) allow the inclusion of affective (psychiatric) illnesses"* (Psychol Med 1995: 25(5):907-916).

Furthermore, on 12th May 2004 the Parliamentary Under Secretary of State at the Department of Health, Dr Stephen Ladyman, announced at an All Party Parliamentary Group on Fibromyalgia (FM) that doctors were being offered financial inducements to persuade patients with FM to attend a "CFS" Clinic to aid recruitment to the PACE Trial. FM is classified by the WHO ICD-10 at M79, whilst ME/CFS is classified at G93.3. For achievement of the recruitment target to have to depend on financial inducements to clinicians in order to persuade patients who do not suffer from ME/CFS to enter the PACE Trial indicated that something was seriously wrong with the trial.

Moreover, by letter dated 14th July 2006 to the West Midlands Multicentre Research Ethics Committee (MREC), Peter White requested permission to advertise (his word) the PACE Trial to GPs. The Investigators were really struggling to recruit participants so decided to recruit patients direct from primary care. The wording of the advertisement to GPs is interesting: *"If you have a patient with*

definite or probable CFS/ME, whose main complaint is fatigue (or a synonym), please consider referring them to one of the PACE Trial centres". Just how scientifically rigorous is the inclusion of patients with "probable CFS/ME" or "fatigue (or a synonym)" was not addressed by Lord Winston.

Quite certainly, such broad canvassing resulted in someone who had shingles (herpes zoster) being included in the PACE Trial on "CFS/ME": since the Oxford criteria catch anyone who is chronically "fatigued", people with post-herpetic tiredness are known to be included in the PACE Trial, even though herpes zoster is not the same disorder as ME/CFS. Such lack of exactitude means that the results of the PACE Trial are unscientific.

In summary, the PACE Trial Investigators intentionally mixed at least three taxonomically different disorders in the trial cohort which Lord Winston described as being "*extremely rigorous entry*" criteria -- those who the Investigators claim to suffer from ME (ICD-10 G93.3); those with fibromyalgia (ICD-10 M79.0) and those with a mental/behavioural disorder (ICD-10 F48.0).

It seems only too obvious that Lord Winston had simply been fed with a script by those involved with the PACE trial and knew little about the subject under debate.

Lord Winston then made an illogical statement: "*Unlike most previous studies, I think I am right in saying that – perhaps the noble Lord, Lord Alderdice, will correct me if I am wrong -- there was only one drop-out, which is fairly remarkable. It means that it is extremely comprehensive, so there are very good data*". It does not follow that, depending on the number of drop-outs, the study was "*very comprehensive*" nor that "*there are very good data*".

Lord Alderdice did not correct Lord Winston, who was indeed wrong and he clearly had not understood The Lancet paper; the PIs themselves provided the following data on drop-outs from treatment: 17 participants (11%) dropped out of the CBT group; 10 participants (6%) dropped out of the GET group; 11 participants (7%) dropped out of the APT group and 14 participants (9%) dropped out of the standardised medical care group.

Moreover, Lord Winston was incorrect to claim that "*there are very good data*": data on the six minute walking test was available for only 69%-76% of participants, a completion figure roughly 20% lower than for other secondary outcome measures, for which the PIs offer no explanation, but if participants dropped out because of ill-health, then the results are skewed in favour of the best-scoring participants.

Lord Winston then informed their Lordships that CBT is effective in "*something like one fifth of patients, which is a bit more successful than the noble Baroness claims*". Apart from the discourtesy of referring to the Countess of Mar as a Baroness, Lord Winston had not done his homework. The figures presented by Lady Mar came from PIs' The Lancet paper and were accurate, namely that only 15% of those who underwent CBT and GET made a moderate improvement (working on the PIs' number needed to treat of 7).

Lord Winston then made a plea on behalf of the PIs for more funding for CBT and GET trials, saying: "*were cognitive behavioural therapy to be used on a slightly more financially secure footing with rather more sessions, it would be likely to be of more benefit*". That is conjecture and it is also illogical: on one hand he said about the PACE trial that it was: "*extremely comprehensive*"; that "*there are very good data*"; that "*I commend this study. It is an example of really excellent research*" and that "*the authors are to be congratulated on demonstrating clearly that cognitive behavioural therapy...is a real improvement on what has happened for these patients before*" but then said that more data are needed.

Naming Myra McClure and Esther Crawley as well as Simon Wessely as victims (Lord Winston referred to Dr Esther Crawley as "*Esther Cranley*", and this can be clearly seen on YouTube), he went on to introduce the topic of the alleged vilification of his colleagues by patients with CFS/ME which, in a debate supposedly about the effects of the PACE trial on CFS/ME patients, was inappropriate. It is, however, a recurring theme used by Wessely to discredit by implication all CFS/ME patients and those clinicians and medical scientists who support their view that it is not a psychosocial but a primary biomedical disorder. Does Lord Winston see legitimate, rational criticisms of the PACE trial made by the Countess of Mar, Professor Malcolm Hooper, consultant physician Dr William Weir and others in the UK, as well as by many international experts, as "vilifying" the psychiatrists who espouse the

psychosocial model of CFS/ME? Despite being requested, no evidence of alleged death threats to Wessely or of related Police crime numbers has been provided.

As for the threats allegedly suffered by Professor Myra McClure and Dr Esther Crawley, whilst a few desperate patients may have given vent to their understandable frustration (particularly at the triumphant way in which Myra McClure's negative XMRV retroviral studies were proclaimed), it seems the "death threats" may be a matter of interpretation. Quite certainly, it is known that Professor McClure has dealt with a correspondent's valid concerns about her work by sending a receipt six weeks later which said *"Your message was deleted without being read"* and Dr Crawley admitted in a radio broadcast in July 2011 that she had not received explicit death threats but had misinterpreted one email to constitute a death threat and that her local police force had taken no action (<http://www.bbc.co.uk/iplayer/console/b012nlcv>).

Lord Winston then made perhaps the most outrageous of his false assertions by referring to CFS/ME in terms: *"these vague conditions appear almost certainly to have a psychiatric basis"*.

That is a profoundly erroneous statement: ME is a defined disorder and has been classified as a neurological disorder by the WHO since 1969; on 16th August 1992, the Rt Hon Stephen Dorrell MP, Minister of Health, went on public record confirming that *"ME is established as a medical condition"* and the Department of Health accepts it as a chronic neurological disorder; since 2003 CFS/ME has been classified in the UK Read Codes used by all GPs as a neurological disease at F 286; since its inception in March 2005 the UK National Service Framework on chronic neurological conditions includes CFS/ME and the Department for Work and Pensions has confirmed in writing that it does not consider ME to be a mental disorder (letter of 21st November 2011 to the Countess of Mar signed by Lord Freud, Minister for Welfare Reform).

Lord Winston finished his speech by saying that the PACE study was: *"an example of really excellent research...done very well indeed...The authors are to be congratulated...."*. Nothing could be further from the truth:

- the premise upon which the trial was based had already been scientifically disproved by the existing biomedical evidence-base, hence it should never have taken place
- both the methodology and the conclusions were flawed
- the primary outcome measures were dropped
- ratings that would qualify a participant as sufficiently impaired to enter the trial were deemed by the Principal Investigators to be "within the normal range" when recorded on completion of the trial
- there were significant conflicts of interest in that all three PIs work for the permanent health insurance industry (whose managers insist that claimants undertake a course of CBT and GET -- called "rehabilitation" -- which, if people are too ill to do so or if they know from their own experience that it makes worse and therefore decline, results in payments being stopped on the basis that claimants do not want to get better)
- the PIs intentionally studied a heterogeneous population
- it was conceded only after publication of selective results in The Lancet that the Investigators did not purport to be studying ME but simply chronic "fatigue"
- there was a failure to control the trial
- there was downgrading of what constituted serious adverse events
- there were many changes to the entry criteria
- data was not reported
- objective outcome measures were dropped
- methods of scoring were changed so as to produce (minimally) statistically better results that were blatantly misreported in The Lancet.

As one ME support group leader, Peter Rubery, commented:

"When I listened to the debate replay I thought that Countess of Mar did a very good job. However I was most surprised that Lord Winston, far from answering the myriad of faults she described with the PACE trial, merely read a script, obviously written by Wessely, praising the care that had been taken in designing and completing the trial. The establishment have certainly got this well and truly tied up".

2. Lord Alderdice

Following Lord Winston, Lord Alderdice appeared to take a more moderate and balanced stance (he was honest enough to admit: *"We really do not know what we are dealing with"*) but his account of how, when he was using CBT for depressed patients, they improved when he persuaded them to get out of bed and do something (*"Hey presto...the thing they felt would not make them better actually did"*) implied that he considers CFS/ME is likewise a psychological condition. It also showed that he had no understanding of the cardinal feature of CFS/ME, namely an inability to produce sufficient energy on demand, a feature that is well-documented and explained in the medical literature.

If he had listened to the Countess of Mar, Lord Alderdice would have heard her say that the biomedical evidence undermines the psychosocial model, but he did not address this.

Lord Alderdice said: *"Certainly, to conclude that there is a definite organic basis....does not mean that we dismiss the psychological – on the contrary"*; he was misrepresenting the issue: the CFS/ME community of patients, carers and those clinicians and researchers who support them do not dismiss the fact that psychological factors affect patients with this disease as with all other diseases. What they dismiss is the psychiatrists' insistence that CFS/ME is perpetuated by patients' aberrant illness beliefs and deconditioning and the repeated claim that it can be reversed or even cured by "cognitive restructuring" (ie. brain washing), because the international biomedical evidence comprehensively disproves such a view.

Lord Alderdice then said: *"The prognosis is variable with different people"*; he was wrong: the prognosis in true ME is predictable; it is a life-long condition from which recovery is unlikely. According to US statistics provided by the Centres for Disease Control (CDC), only 4% of patients with CFS/ME had full remission (not recovery) at 24 months (US CDC CFS Programme Update, 29th August 2001).

In that same year, the Scottish Parliament was provided with statistics showing that 80% do not ever recover (Dr Abhijit Chaudhuri, Senior Clinical Lecturer in Neurology, University of Glasgow, 4th April 2001).

International expert Dr Daniel Peterson from the US has stated about CFS/ME: *"In my experience, (it) is one of the most disabling diseases that I care for, far exceeding HIV disease except for the terminal stages"* (JCFS 1995:1:3-4:123-125).

At the Press Briefing held on 3rd November 2006 by the US Centres for Disease Control to announce its CFS/ME awareness campaign, two eminent professors who specialise in CFS/ME spoke on public record about the nature of CFS/ME. Anthony Komaroff, Professor of Medicine, Harvard Medical School, said:

*"It's a pleasure to be here today with several people who have dedicated successfully a big part of their lives to trying to understand and **get recognition for this terrible illness.***

"It's not an illness that people can simply imagine that they have and it's not a psychological illness. In my view, that debate, which was waged for 20 years, should now be over.

***"Brain imaging studies...have shown inflammation, reduced blood flow and impaired cellular function in different locations of the brain"**..*

***"Today we have powerful new research technologies and tools we didn't have even 20 years ago, and they are being put to good use by laboratories all over the world"**.*

Nancy Klimas, now Professor of Medicine, Professor and Chair, Department of Clinical Immunology; Scientific Director, Institute for Neuroimmune Medicine, Nova Southeastern University, but at the time Professor of Medicine and Immunology at the University of Miami (who was then President of the International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis, an organisation of medical professionals and research scientists), said:

*"Today there is evidence of the biological underpinnings. **And there's evidence that the patients with this illness experience a level of disability that's equal to that of patients with late-stage AIDS, patients undergoing chemotherapy, patients with multiple sclerosis.***

"And that has certainly given it a level of credibility that should be easily understood.

"We need to educate physicians and other health care workers about this illness so that every single doctor...knows the diagnostic criteria.

"There are diagnostic criteria that enable clinicians to diagnose (ME)CFS in the primary care setting".

Professor Klimas is also on record:

"I hope you are not saying that (ME)CFS patients are not as ill as HIV patients. I split my clinical time between the two illnesses, and I can tell you that if I had to choose between the two illnesses I would rather have HIV" (New York Times, 15th October 2009).

Lord Alderdice went on to say: *"It is terribly important that we try to evaluate how to manage the problems that people come along to us with"*; what he and the other speakers after Lady Mar failed to understand is that the type of CBT used in the PACE trial is not supportive as in helping sick people to manage a life-changing condition, but directive (ie. it is specifically directed at changing the way patients think about their illness with the intention of convincing them they do not suffer from a physical disorder, but from reversible deconditioning). Indeed, Simon Wessely has publicly stated: ***"CBT is directive – it is not enough to be kind or supportive"*** (New Statesman, 1st May 2008). This is a very important point.

Lord Alderdice spoke about what patients themselves think will help: *"Sometimes they are intuitively right and sometimes they are intuitively mistaken"*; the fact that patients with CFS/ME are so against the type of CBT and GET used in the PACE trial has nothing to do with intuition but is based on experience and medical science.

In 1990, one UK researcher, Dr Darrel Ho-Yen, Head of Microbiology, Raigmore Hospital, Inverness, referring to Wessely's paper "Management of chronic (postviral) fatigue syndrome" (JRCGP 1989:39:26-29) wrote: ***"It has been suggested that a new approach to the treatment of patients with postviral fatigue syndrome would be the adoption of a cognitive behavioural model. Those who are chronically ill have recognised the folly of the approach and, far from being maladaptive, their behaviour shows that they have insight into their illness"***. (Patient management of the postviral fatigue syndrome DO Ho-Yen (JCGP 1990:40:37-39)

Lord Alderdice went on to say that CBT and GET are *"probably not completely helpful to almost anybody....There are a lot of scientific tables and graphs but that is the basic outcome"*. Indeed so: CBT/GET are not completely helpful to almost anybody.

Like Lord Winston, Lord Alderdice had clearly been primed by the same source, as evidenced by his statements that: *"It is really important that when people give themselves to scientific enterprise in this area that we do not pillory them for their efforts"* and *"we should not pillory people who come in because that only drives people out of research"*.

International clinicians and medical scientists who disagree with Wessely and White et al do so because they object to methodologically flawed studies. As Lady Mar pointed out in her opening speech, Dr Ben Goldacre stated: *"in a trial... you have to say which is the "primary outcome" before you start: you can't change your mind about what you're counting as your main outcome.... It's not just dodgy, it also messes with the statisticsYou cannot change the rules after the game has*

started. You cannot even be seen to do that" (The data belong to the people who gave it to you: The Guardian: 5th January 2008).

The fact is that the PACE PIs did "change the rules after the game has started" and they have "been seen to do that".

Having agreed to participate in an area of such controversy, Lord Alderdice should have made sure he was better prepared.

3. Baroness Meacher

Lady Meacher said: "I like to refer to it as a syndrome because it seems to be not one but a number of diseases". She did not say how it could therefore be safe to recommend the same behavioural intervention for a number of diseases with quite different pathophysiology.

This is an important issue: for over 20 years the Wessely School psychiatrists have insisted on making their definition of CFS/ME as wide as possible, with the result that many different disorders now come under that umbrella and the label has become clinically meaningless.

In 1994, Professor Michael Sharpe (a PACE PI), supported by Wessely, stated: "The exclusion of persons (with psychiatric disorders) would substantially hinder efforts to clarify the role that psychiatric disorders have in fatiguing illness" (Ann Intern Med 1994;121:12:953-959) and Professor Anthony Pinching, known for his recommendation of CBT and GET for CFS/ME patients, stated in the 2002 UK Chief Medical Officer's Report on CFS/ME: "It seems appropriate to regard CFS/ME as a single entity...(the question of sub-groups) may be considered a matter of semantics and personal philosophy".

Such a view is not supported by world-renowned CFS/ME researchers, who since at least 1995 have been calling for sub-grouping: sound biomedical research has strengthened the need for it because the label "CFS" has become so heterogeneous, and biomedical experts recognise that researchers must sub-group patients by features including chronicity, immunological profiles and neuroendocrine dysfunction and must cease to conflate CFS/ME with chronic "fatigue" (Concepts of Accountability, pp 17 – 23; http://www.meactionuk.org.uk/CONCEPTS_OF_ACCOUNTABILITY.htm).

In 1997, a Review article by Jason et al found that flaws in the case definition and in the design of early epidemiological studies have led to "inaccurate and biased characterisations of (ME)CFS" which incorrectly favour a psychiatric view of the disorder. The authors were clear: "**The erroneous inclusion of people with primary psychiatric conditions in (ME)CFS samples will have detrimental consequences for the interpretation of both epidemiologic and treatment efficacy findings. Until more differentiated subgroups are developed, it will be exceedingly difficult to identify characteristics that are common for all people with the diagnosis of (ME)CFS**" (American Psychologist 1997;52(9):973-983).

In 1998, a report of an Australian international conference on (ME)CFS held in Sydney on 12th –13th February noted the recommendation for "fully informing the medical profession..... to increase competence in diagnosis (and to include (ME)CFS) in the medical student/training curriculum'.. **The guidelines are also intended to 'redress the harm and distress caused by inappropriate psychiatric referral, placing such misdiagnosis in the context of malpractice in terms of duty of care'**" (Lancet 1998;351:574).

In 1999, Jason et al noted: "Chronic fatigue syndrome is one of the most debilitating medical conditions when quality of life indicators such as those measuring quality of relationships, financial security, and health status are used. **Many physicians believe that most patients with this disease are suffering from a psychiatric illness. These biases have been filtered to the media, which has portrayed chronic fatigue syndrome in simplistic and stereotypic ways. Due to the controversy**

surrounding a chronic fatigue syndrome diagnosis, people with this illness are sometimes overwhelmed with disbelieving attitudes from their doctors, family and/or friends, and many experience profound losses in their support systems" (AAOHN J. 1999:47(1):17-21).

In 2005, Stein was emphatic that the Oxford criteria (created and used by the Wessely School and used in the PACE trial) fail to exclude patients with primary psychiatric diagnoses and are not often used by other researchers. The symptoms of (ME)CFS occur in multiple organ systems and no other disorder can account for the symptoms. Stein was outspoken: ***"Despite the preponderance of research to the contrary, a group of primarily British psychiatrists continue to publish that (ME)CFS is caused and exacerbated by faulty self-perception and avoidance behaviour. The faulty beliefs are described as: 'the belief that one has a serious disease; the expectation that one's condition is likely to worsen; (patients with (ME)CFS adopt) the sick role; and the alarming portrayal of the condition as catastrophic and disabling'. It should be noted that neither this paper nor any of the others with similar views are evidence-based – they are the personal opinions of the authors. Those who think of (ME)CFS as 'fatigue' and forget the importance of the other symptoms will be at risk of misdiagnosing patients leading to inappropriate treatment recommendations. CBT to convince a patient that s/he does not have a physical disorder is disrespectful and inappropriate....The rationale of using CBT in ME/CFS is that inaccurate beliefs and ineffective coping maintain and perpetuate morbidity (but) it has never been proven that these illness beliefs contribute to morbidity in (ME)CFS"*** (www.mefmaction.net).

Also in 2005, Jason et al were unequivocal: ***"Review of further findings suggests that subtyping individuals with CFS on functional disability, viral, immune, neuroendocrine, neurology, autonomic and genetic biomarkers can provide clarification for researchers and clinicians. Subgrouping is the key to understanding how CFS begins, how it is maintained, how medical and psychological variables influence its course, and in the best case, how it can be prevented, treated and cured"*** (Neuropsychology Review 2005:15:1:29-58).

In 2006, Demitrack encapsulated the problem of the Wessely School's overly-inclusive approach: ***"The role of clinical methodology in the study of therapeutics is not trivial, and may confound our understanding of recommendations for treatment". Demitrack noted the various studies by certain psychiatrists purporting to show that the likelihood of psychiatric disorder increased with the number of physical symptoms. He noted that: "The most extreme view considers these observations to provide convincing evidence that (ME)CFS is, in essence, embedded in the larger construct of affective disorders". However, in relation to (ME)CFS, he noted that: "The observation of specific protracted fatigue and the absence of substantial psychiatric comorbidity argues convincingly that this is an inappropriate and overly simplistic way of approaching this puzzling condition....In the face of accumulating evidence, there is an increasing realisation that a unitary disease model for this condition has been a theoretical and practical impediment to real progress towards effective therapeutics for (ME)CFS. Many treatment studies have, unfortunately, neglected to thoroughly consider the significance of patient selection (and) symptom measurement"*** (Pharmacogenomics 2006:7(3):521-528).

Also in 2006, Jason et al stated: ***"Grouping all individuals who meet diagnostic criteria together is prohibiting the identification of these distinct biological markers of the individual subgroups. When specific subgroups are identified, even basic blood work may reveal a typical pattern of abnormality on diagnostic tests....The identification of clinically significant subgroups is the next logical step in further CFS research. Previous research examining people with CFS as a homogeneous group may have missed real differences among subgroups of this illness"*** (Exploratory Subgrouping in CFS: Infectious, Inflammatory and Other. In: Advances in Psychology Research 2006:41:115-127. A Columbus (Ed): Nova Science Publishers, Inc).

A significant study which does not support combining all states of "medically unexplained fatigue" into a single somatoform disorder is that of Jason et al which provides clear evidence of how different subgroups of "CFS" may respond to nonpharmacologic interventions such as CBT: ***"Early researchers describing nonpharmacologic behavioural interventions for CFS reported high levels of success but***

more recent studies have had somewhat more mixed results.....***Those individuals with most impaired hypothalamic-pituitary-adrenal axis (HPA) function might be the least able to improve with nonpharmacologic interventions....It is possible that some individuals with CFS have a cortisol deficiency and others do not, but when all are combined into one large CFS category, these important differences are ignored....This study suggests that subgrouping according to endocrinologic functioning is a useful strategy for assessing the effects of treatment***" (Baseline Cortisol Levels Predict Treatment Outcomes in Chronic Fatigue Syndrome Nonpharmacological Clinical Trial. JCFS 2007;14:4:39-59).

The above are merely a few illustrations from the substantial evidence-base that does not support the PACE PIs' overly-inclusive *modus operandi*.

Baroness Meacher went on to say that: *"NICE compares the physical symptoms of CFS/ME with those of multiple sclerosis, systemic lupus erythematosus...and rheumatoid arthritis, probably three of the most fearsome illnesses one can think of"* but did not say that patients suffering from the same symptoms but who had been given one of those disease labels are not subjected to directive cognitive re-structuring to make them change the way they think about their symptoms.

She then said she awaited the outcome of Professor White's cytokine research later this year, but seemed unaware that nine years ago he published his own cytokine research which showed that:

- ***"Immunological abnormalities are commonly observed in CFS...Concentrations of plasma transforming growth factor-beta (TGF- β) (anti-inflammatory) and tumour necrosis factor-alpha (TNF- α) (pro-inflammatory) have both been shown to be raised....Abnormal regulation of cytokines may both reflect and cause altered function across a broad range of cell types....."***
- ***"Altered cytokine levels, whatever their origin, could modify muscle and or neuronal function.... Concentrations of TGF- β 1 were significantly elevated in CFS patients at all times before and after exercise testing..."***
- ***"We found that exercise induced a sustained elevation in the concentration of TNF- α which was still present three days later, and this only occurred in the CFS patients...."TGF- β was grossly elevated when compared to controls before exercise (and) showed an increase in response to the exercise entailed in getting to the study centre...."***
- ***"The pro-inflammatory cytokine TNF- α is known to be a cause of acute sickness behaviour, characterised by reduced activity related to 'weakness, malaise, listlessness and inability to concentrate', symptoms also notable in CFS....."***
- ***"These...data suggest that 'ordinary' activity (ie. that involved in getting up and travelling some distance) may induce anti-inflammatory cytokine release (TGF β), whereas more intense exercise may induce pro-inflammatory cytokine release (TNF- α) in patients with CFS" (JCFS 2004:12 (2):51-66).***

From his own study, the Chief PI knows that TNF α remains elevated three days after exercise in ME/CFS patients. No mention of this, or of the demonstrated need for pre- and post-exercise testing for raised cytokines, was made in the PACE trial. In the light of this knowledge, there seems to have been a disregard of safety for GET participants.

Baroness Meacher then repeated her previous view: *"The experts believe that in time a number of distinct diseases will be identified that currently fall within the CFS/ME label"* but she failed to address Lady Mar's question of how safe is it to use the same intervention for treating distinctly different diseases.

Lady Meacher appeared to have been primed by the same source because she produced the well-worn Wessely School mantra about CBT and GET being: *"the interventions for which there is the clearest evidence of benefit to patients"*, seemingly unaware that this is not the case. There is abundant evidence from numerous professionally-analysed surveys by CFS/ME charities of almost 5,000 patients that in such patients CBT is ineffective and that GET is unacceptable and sometimes positively harmful.

Those surveys include one sponsored jointly by the ME Association and Action for ME ("Report on a Survey of Members of Local ME Groups". Dr Lesley Cooper, 2000). Cooper found that *"Graded exercise was felt to be the treatment that made more people worse than any other"* and that it had actually harmed patients

(<http://www.afme.org.uk/res/img/resources/Group%20Survey%20Lesley%20Cooper.pdf>).

Another survey of 2,338 CFS/ME sufferers ("Severely Neglected: M.E. in the UK") was carried out in 2001 by Action for ME; its preliminary report stated: *"Graded exercise was reported to be the treatment that had made most people worse"*; in the final report, this was changed to stating that graded exercise had made 50% of patients worse

(<http://www.afme.org.uk/res/img/resources/Severely%20Neglected.pdf>).

The 25% ME Group for the Severely Affected carried out a further survey in 2004 which found that 93% of respondents found GET to be unhelpful, with 82% reporting that their condition was made worse

(<http://www.25megroup.org/Group%20Leaflets/Group%20reports/March%202004%20Severe%20ME%20Analysis%20Report.doc>).

In 2005, a report ("Our Needs, Our Lives") published by The Young ME Sufferers Trust found that 88% had been made worse by exercise (<http://www.tymestrust.org/pdfs/ourneedsourlives.pdf>).

In June 2007, through Section 16b funding from the Scottish Government, Action for ME produced a report "Scotland ME/CFS Scoping Exercise Report", which found that 74.42% were made worse by GET.

In 2008, Action for ME published another survey of over 2,760 patients ("M.E. 2008: What progress?") which found that one third had been made worse by GET and that at their worst, 88% were bed/housebound, being unable to shower, bathe or wash themselves, and that 15% were unable to eat unaided. The Press Release of 12th May was unambiguous: *"Survey finds recommended treatment makes one in three people worse"* (<http://www.afme.org.uk/news.asp?newsid=355>).

In 2009, the Norfolk and Suffolk ME Patient Survey of 225 respondents stated: *"Respondents found the least helpful and most harmful interventions were Graded Exercise Therapy and Cognitive Behavioural Therapy"* (<http://www.norfolkandsuffolk.me.uk/surveylink.html>).

There have been numerous clinical trials of CBT/GET for patients with CFS/ME which came to very different conclusions about its efficacy than the Wessely School psychiatrists, for example:

In 1999, Fred Friedberg, Clinical Assistant Professor, Department of Psychiatry and Behavioural Science, State University of New York, pointed out the differences between CBT trials in England and the US: *"Several studies of graded activity-orientated cognitive behavioural treatment for CFS, all conducted in England, have reported dramatic improvements in functioning and substantial reductions in symptomatology. On the other hand, cognitive behavioural intervention studies conducted in Australia and the United States have not found significant improvements in functioning or symptoms. Descriptive studies of CFS patients in England, the US and Australia suggest that the CFS population studied in England shows substantial similarities to depression, somatization or phobia patients, while the US and Australian research samples have been clearly distinguished from primary depression patients and more clearly resemble fatiguing neurological illnesses. Because successful trials have all been conducted in England, a replication of these*

findings in a well-designed US study would be necessary before a general recommendation for graded activity / CBT could be made" (JCFS 1999:5: 3-4:149-159).

The 2000 Cochrane Collaboration review of the literature on CBT for CFS found: ***"There is no satisfactory evidence for the effectiveness of CBT in patients with the milder form of CFS found in primary care or in patients who are so disabled that they are unable to attend out-patients. Additionally, there is no satisfactory evidence for the effectiveness of group CBT"***.

In 2001, it was shown that the very modest benefit in only some CFS/ME patients who had undergone CBT lasted for only 6-8 months and ***"observed gains may be transient"*** (Long-term Outcome of Cognitive Behavioural Therapy Versus Relaxation Therapy for Chronic Fatigue Syndrome: A 5-Year Follow-Up Study. Alicia Deale, Trudie Chalder, Simon Wessely et al. Am J Psychiat 2001;158:2038-2042)

In January 2002, psychiatrist Alan Gurwitt who has been seeing patients with (ME)CFS since 1986 published ***"Pseudo-science"*** in which he summed up the problem in the UK: ***"I have often been embarrassed by and angry at many of my colleagues who fall in line with self-declared 'experts' who see somatisation everywhere. Ever since the mid-1980s there have been 'researchers' with an uncanny knack at cornering research funds because of their already-formed biases that are in synch with the biases of the funding government organisations (and who) indicate that CBT and graded exercise will do the therapeutic job, thus implying a major psychological causative factor. I have noticed the following deficits in their work, their thinking, their word choices and their methods:***

- *They often fail to distinguish between 'chronic fatigue' and CFS*
- *They fail to distinguish between pre-illness psychological functioning and post-onset occurrence of reactive symptoms. This error would disappear if they did thorough psychiatric evaluations. Their failure to do proper in-depth psychiatric evaluations in at least some of their studies is a serious error with drastic implications*
- *Their studies make use of flawed, inappropriate and superficial tests of psychological state which then lead to flawed, inappropriate and superficial conclusions. Their use of large numbers of study subjects gives the impression that they are scientific; in my view it is pseudo-science*
- *They fail to include, or to be aware of, the mounting medical-neurological-immunological evidence demonstrating the medical nature of (ME)CFS*
- *They demonstrate instead a morbid preoccupation with psychiatric morbidity"* (Co-Cure ACT 11th January 2002).

In 2003, in his Summary of the 6th AACFS International Conference in 2003, Charles Lapp, Associate Clinical Professor, Duke University and Director, Hopkins-Hunter Centre, NC, stated about CBT that Dr Daniel Clauw (who had studied 1,092 patients) found that at 3 months there were modest gains, but at follow-up at 6 and 12 months, those modest gains were lost.

Huibers and Beurskens et al's findings were unequivocal: ***"There was no significant difference between the experimental group and the control group on primary or secondary outcomes at any point. Cognitive behavioural therapy by general practitioners for unexplained, persistent fatigue did not prove to be an effective intervention"*** (Brit J Psychiat 2004;184:240-246).

In 2005, Canadian psychiatrist Dr Eleanor Stein stated: ***"It is important to note that no CBT study has reported that patients have improved enough to return to work, nor have they reported changes in the physical symptoms. Despite the fact that worsening of symptoms after exercise is a compulsory criterion for diagnosis of ME/CFS, graded exercise programmes have often been prescribed for such patients (but) neither exercise tolerance nor fitness has been shown to improve with exercise programmes. The medical literature is clear that ME/CFS is not the same as any psychiatric disorder"*** (Chronic Fatigue Syndrome: Assessment and Treatment of Patients with ME/CFS: Clinical Guidelines for Psychiatrists (www.mefmaction.net)).

Jason et al are clear: *“Despite improvement found in a number of interventional studies (referring to Wessely School studies), other studies have been less successful. Furthermore, **physician-delivered CBT for CFS participants has not shown efficacy in two studies. In 2001, Ridsdale et al found that counselling was as effective as CBT... The changes in the present trial were relatively modest and few participants experienced remission of illness**”*. The authors also note the lack of long-term effects when the (very high) drop-out rates are taken into consideration (J Clin Psychol Med Settings 2007;14:4:275-296).

Following rigorous analysis, Malouff et al noted the drop-out rates (up to 42%) and concluded: *“One can conclude that CBT for chronic fatigue disorders has about the same efficacy as diverse psychological treatments for a variety of psychological disorders. **There presently appears to be no empirical basis for including cognitive components in treatment of fatigue disorders**”* (Efficacy of cognitive behavioural therapy for chronic fatigue syndrome: A meta-analysis. Clinical Psychology Review. 2007. Doi:10.1016/j.cpr.2007.10.004).

A later (2008) Cochrane Collaboration Intervention Review of CBT for CFS (Jonathan Price et al. Cochrane Database of Systematic Reviews, vol. 16 #3, July 2008. John Wiley & Sons) **concluded that results were inconsistent, making it difficult to draw any conclusions. At follow-up, there was no difference between CBT and usual medical care.**

Lady Meacher made no mention of any of this evidence.

Quoting the Pls' latest paper in Psychological Medicine (1st April 2013), Baroness Meacher said it was a great step forwards that 22% of patients had recovered. Whilst she acknowledged that there is debate about the word “recovery”, she failed to say that the Pls used three different definitions of “recovery” and that their definition of “recovery” does not mean the absence of disabling symptoms.

Lady Meacher went on to say: *“I understand that my noble friend Lady Mar respects the PACE study but, very reasonably in my view, has grave concerns about the spin put upon the results”*. Lady Mar does not respect the PACE study at all; she has consistently expressed her dismay about its seriously flawed methodology. Over 2,000 pages of internal information about the PACE trial were obtained under an early FOIA request (similar FOIA requests by others have since been refused) and the evidence those pages contain -- including Minutes of the Trial Steering Committee, Minutes of the Data Monitoring and Ethics Committee and correspondence between Professor White and the West Midlands Multicentre Research Ethics Committee about changes to the original protocol -- entirely justifies her concerns.

Baroness Meacher then acknowledged that: *“In terms of returning to work, the PACE trial had no effect whatever on the numbers of CFS/ME patients in work”* but she then said: *“the social care costs and the need for family support were reduced”* without acknowledging what Lady Mar had said, namely that claims for income-related benefits, illness and disability related benefits and private pensions and income protection claims had all increased across all intervention groups. Had participants recovered, they could have been defined as being recovered and available for work were it to be available, but none was so identified by the Pls.

Lady Meacher said: *“We know that serious life events or further infections do – or can – cause relapses in this horrible set of illnesses of this syndrome”* but the PACE Pls treated *“this horrible set of illnesses”* as one single entity that is perpetuated by aberrant illness beliefs.

Like the other speakers who praised the PACE trial, Lady Meacher did not address the fact that because of the impenetrable obfuscation used by the Pls in their selective reporting of the outcome, it is impossible to know if those who “recovered” suffered from true ME with its devastating neuroimmune and cardiovascular dysfunction or simply from idiopathic chronic fatigue.

She said that she had been reliably informed that 51% of PACE participants had been defined as having ME rather than CFS, but she did not mention the fact the Chief PI has confirmed to the editor-in-chief of The Lancet in writing that his trial did not purport to be studying CFS/ME, but only people whose main symptom was “fatigue”.

Equally she did not mention that the PIs defined those with “ME” by using their own modification of the London criteria (which, unscientifically, did not require the cardinal feature of true ME -- post-exertional malaise -- to be present for a diagnosis of ME), yet the PIs claimed that people with ME had indeed recovered. Unless one has detailed knowledge of exactly how the PACE trial methodology was manipulated, it is not possible to grasp just how duplicitous the PIs have been. In clinical trials, definition is critical.

Lady Meacher went on to state: *“There is no indication that CBT or GET caused any problems”* but she failed to say that the PIs down-graded their definition of serious adverse events so that they consisted only of death or a life-threatening event necessitating hospital admission.

She said that the PACE trial: *“has received acclaim from clinicians and scientists across the world”* but failed to say that such acclaim came from those who hold the same view as the PIs and Wessely about the psychosocial nature of CFS/ME, or that it received cogent international criticism from medical scientists whose research has compellingly disproved the psychosocial model of CFS/ME.

Baroness Meacher then spoke about the changes made by the PIs to their original protocol; she said *“the changes were minor and did not affect the results or conclusions in any significant way”*. Lady Meacher herself could have had no idea about this, so this statement was obviously fed to her by those associated with the PACE trial. Contrary to her statement, the changes were very definitely not minor but were of major significance, as confirmed by the information obtained under an FOIA request. They included very significant changes, amongst other things:

- the abandonment of the definition of recovery as set out in the protocol: this means that a physical function score (SF-36) of 85 was reduced by 25 (twenty five) points down to 60 (ie. a lower score than that required for entry to the trial); the fatigue score was also changed such that a participant could have worse fatigue at outcome than entry
- alterations to the entry criteria: when recruiting began, a threshold of 60 on the SF-36 physical function scale was adopted. Because of recruitment difficulties, eleven months after the trial began, ***“this requirement was changed from a score of 60 to a score of 65 to increase recruitment”***. This meant that the first tranche of participants met different entry criteria from those who were recruited later. This change has important implications for the analysis of the results
- the dropping of post-therapy actigraphy: participants wore an actometer at the beginning of the trial but the Chief PI decided participants should not wear one at the end of the trial
- the down-grading of what constituted a serious adverse events
- the change of fatigue outcome reporting: at outset, bimodal scoring was used, but once under way, this was changed to Likert scoring, making interpretation impossible without access to the actual data
- the modification of the “London” criteria so that the cardinal symptom of true ME was deemed unnecessary for a diagnosis of CFS/ME.

None of these changes can be described as “minor”.

Lady Meacher then said these changes were made before analysis of the data and that they had been approved by *“the independent trial steering committee”*. The trial steering committee was not, however, “independent”. It included Professor Tom Sensky from the Division of Neurosciences and Mental Health, Imperial College, London, who is, like Simon Wessely, a liaison psychiatrist who believes in the effectiveness of cognitive behavioural therapy.

At the launch of The Psychological Medicine Network on 10th December 2004 at Regent’s Park College, Sensky’s presentation was entitled *“Somatisation and Primary Care”*, and he made some disturbing statements about patients with medically unexplained symptoms (MUS) in which he includes CFS/ME patients. His PowerPoint slides (some of which have now been removed from the internet but which have been downloaded and kept) state, for example, that:

- *“People who present with somatisation disorders are often difficult to manage (and) may arise (sic) strong feelings in clinicians”*
- *“Difficulties in Doctor – Patient Relationship: Correlations with Number of Somatoform Symptoms (extent of frustration with patient’s symptoms; perception that patient is manipulative)”*
- *“Correlations with GP Clinical Grading of Somatisation (helpless behaviour of patient; tiresome patient; difficult patient)”*
- *“Attitudes of GPs toward patients with medically unexplained symptoms (they are difficult to manage; they have personality problems; they have a psychiatric illness)”*.

In his slide *“GPs’ Views: irritable bowel and CFS compared”*, Sensky states that IBS patients have an anatomical or physiological basis for their symptoms but there is no such basis in CFS/ME; that IBS patients do not have a low threshold for symptoms but that CFS/ME patients do have a low threshold for symptoms; that IBS patients do not lack stoicism but that CFS/ME patients do lack stoicism, and that IBS patients do not transgress the obligations of the sick role but CFS/ME patients do transgress it.

Sensky maintains that GPs make *“inappropriate referrals”* for patients with medically unexplained symptoms and teaches that GPs should make *“persuasive statements”* to patients with MUS in the form of *“Provision of a ‘non-disease’ explanation of the patient’s symptoms”*.

His slides state that interventions for somatoform disorders should include *“reattribution”* of the patient’s presenting symptoms and he gives as an example: *“I feel my heart pounding in my chest”*, which he dismisses as somatic (he makes no mention of the possibility of autoimmune thyroiditis or of dysautonomia, both of which could cause a pounding heart and both of which are documented in the literature as occurring in CFS/ME).

It seems that Sensky shares many of the same views about CFS/ME as Professor Sir Simon Wessely and Professor Peter White, so perhaps it is unsurprising that he was involved with their PACE Trial.

Baroness Meacher concluded by saying about conflicts of interest that *“none applied to the statisticians who did the analysis”*. That is untrue.

Dr Tony Johnson, Deputy Director of the MRC Biostatistical Unit, Cambridge, oversaw the PACE Clinical Trial Unit (directed by Professor Simon Wessely) and was a member of the Trial Management Group and a member of the Trial Steering Committee.

The Quinquennial Report for the MRC’s Biostatistical Unit’s progress report for the years 2001 to 2006 was placed on the website of the MRC Biostatistics Unit (BSU).

One part of that report states: *“Our influence on policy-makers has largely been indirect, through scientists’ work on advisory committees, in leading editorials, in personal correspondence with Ministers, Chairs or Chief Executives (such as of Healthcare Commission or NICE), Chief Medical Officers and Chief Scientific Advisers, or through public dissemination when the media picks up on statistical or public health issues that our publications have highlighted.*

“The Unit’s scientists must remain wary of patient-pressure groups. Tony Johnson’s work on chronic fatigue syndrome (CFS), a most controversial area of medical research, has had to counter vitriolic articles and websites maintained by the more extreme charities and supported by some patient groups, journalists, Members of Parliament, and others, who have little time for research investigations”.

This contention that “CFS” research is beset with vitriol and “extreme” charities was re-iterated by Johnson himself in his own Report within the Quinquennial Review which was co-authored by Professor Peter White; under “Chronic Fatigue Syndrome”, Johnson’s Report stated:

“CFS is currently the most controversial area of medical research and characterised by vitriolic articles and websites maintained by the more extreme charities supported by some patient groups, journalists, Members of Parliament, and others, who have little time for research investigations”.

Upon seeing this on the MRC Biostatistics Unit’s (BSU) website, an ME sufferer wrote first to the Head of the MRC Biostatistics Unit and then to Dr Johnson himself, requesting the names and details of all the charities, patient groups, journalists, Members of Parliament and “others” who have little time for research investigations, together with references for all the vitriolic articles and websites mentioned on the MRC BSU website.

Almost a full month later, a letter dated 10th October 2006 was received from Dr Anthony Peatfield, Head of MRC Corporate Governance and Policy, which said: *“You refer to some text that was recently published on the website of the MRC Biostatistics Unit.... **The comments have now been removed from the website.** I would like to take this opportunity to apologise, on behalf of the MRC, for any offence these comments may have caused either to yourself or any other individual”.*

Having taken seven months to reply to a letter that had been sent to him personally, on 7th November 2006 Tony Johnson attempted to exonerate himself, stating that the views he had expressed were not intended to represent the views of the MRC and that they had been *“the initial version of my progress report”*, and he wrote: *“I regret the words that I used”*.

Tony Johnson also stated in his letter: ***“I did not have specific individuals or groups in mind and consequently, I cannot provide you with the names and details of the charities, patient groups, journalists, Members of Parliament, and others, who I believed had little time for research. I do not have, and I have never thought about, attempting to compile such a list. Similarly, I do not possess, and have never possessed, a list of vitriolic articles and websites, so I cannot provide these”.***

In his Report, Johnson had referred disparagingly to *“websites maintained by the more extreme charities”* but did not mention that it was two of the UK’s major charities (The ME Association, to which his mother-in-law Dr Elizabeth Dowsett had been Medical Advisor and of which she had been President, and the 25% ME Group for the Severely Affected) that were calling for the PACE trial to be halted.

The tactics used by the Wessely School psychiatrists to ensure dissemination of their own views were unambiguously set out by Dr Tony Johnson and from this whole episode concerning his BSU Report, the CFS/ME community was left in no doubt about the bitter contempt for sufferers, some charities, and those MPs who support them that exists at the MRC, or about the extent to which the Wessely School psychiatrists and their supporters go to ensure that their view of the nature of CFS/ME is accepted by the Establishment.

The ***“vitriolic articles and websites maintained by the more extreme charities and supported by some patient groups, journalists, Members of Parliament, and others, who have little time for research investigations”*** did not exist, any more than other unsubstantiated but continued allegations of vilification may not exist.

Perhaps Baroness Meacher does not regard overtly expressed contempt for CFS/ME sufferers and fabricated allegations made against them as a conflict of interest by the senior statistician who was responsible for the PACE trial statistics.

4. Lord Layard

Lord Layard began his speech by saying he wanted to focus on treatment, *“as there have been terrible misunderstandings and misperceptions put about on that score”*. From the worldwide literature, it is clear that the misunderstandings and misperceptions have been put about by those UK psychiatrists

who promote CBT and GET, many of whom work for the permanent health insurance industry and who act as advisors to UK Government departments. Because of their influence, patients' adverse experience of those interventions has been disregarded by Government departments and other agencies of the State.

Lord Layard then said: *"the issue of what causes the condition is often quite different from how we can best treat it. This is such a basic point but it is not fully understood by many of the people who suffer from this condition"*. Lord Layard is not medically qualified; he is an economist, so he is not involved in treating patients and cannot know what they understand.

The PACE trial PIs use their own brand of CBT and GET (ie. directive, not supportive) on the basis that the chronicity of CFS/ME is caused by wrong illness beliefs and consequent deconditioning and that without such aberrant illness beliefs, there would be no CFS/ME. They currently believe that, even if the initial cause is a viral infection, perpetuation of the disorder is caused by such wrong perceptions. Lord Layard misinformed their Lordships when he said that many sufferers do not understand what he referred to as *"such a basic point"*. They have far better understanding and, in many cases, far more knowledge of the biomedical literature than either the PIs or Lord Layard himself and know that what is causing CFS/ME is also what is perpetuating it.

He continued: *"This form of treatment implies nothing about what we believe to be the cause"*. That is an erroneous statement: the PIs' form of treatment indicates that they regard the cause of CFS/ME as being aberrant illness beliefs, deconditioning and *"hypervigilance to normal bodily sensations"*.

PACE trial therapists were trained to instruct participants that their symptoms **do not result from physical disease, with the inescapable conclusion that ME/CFS is considered a non-disease. Indeed, the Therapists' Manual on CBT taught therapists how to manage participants who believe they have a physical disease, how to persuade them that this is not the case, and how to dissuade them from seeking further medical attention.**

Lord Layard next referred to *"chronic fatigue"*, but chronic fatigue is not the same as CFS/ME. Fatigue is a symptom, not a disorder.

He continued: *"People who suffer from CFS...are surely making a mistake when they reject psychological support for their condition on the grounds that this implies something about its cause"*. Lord Layard did not tell their Lordships that patients with CFS/ME do not reject it on the basis he put forward but (i) on the basis that the scientific evidence vitiates the PIs beliefs; (ii) on the evidence that CBT and GET are not beneficial but are actually harmful and result in serious relapse, sometimes life-long, and (iii) on their own experience that it does not help. Patients with CFS/ME are desperate to recover: if CBT/GET were successful, patients would be queuing up for it, but it doesn't work.

Lord Layard said: *"In their own interests, they should focus on what is the best possible treatment available on the evidence"*; absolutely true, but CFS/ME sufferers know that the best treatment is not CBT or GET. As mentioned above, Dr Darrel Ho-Yen, Head of Microbiology, Raigmore Hospital, Inverness, said: ***"Those who are chronically ill have recognised the folly of the approach and, far from being maladaptive, their behaviour shows that they have insight into their illness"***. (JCGP 1990:40:37-39)

Lord Layard then said: *"In the meantime, we have a large amount of evidence that both CBT and graded exercise therapy enable many more people to recover than if the only treatment they have is standard medical care"*. This is not true. The PACE trial is the only study to compare CBT/GET with standard medical care. It showed that over and above standard medical care, only 15% of those in the GET/GET groups made a moderate improvement.

Lord Layard went on: *"My main point is that this is so, whatever the definition of recovery"*. "Recovery" does not mean whatever the PIs want it to mean; it means the regaining of full health after sickness, which includes being symptom-free, not being in receipt of State or insurance benefits

and being able to hold down a full-time job or be in full time education, with a pre-morbid level of social, leisure and sporting activities.

Lord Layard did not comment on what the Countess of Mar said, namely that in the PACE trial, a participant could have been enrolled with a physical function score of 65, deteriorate during the interventions to a score of 60, but the interventions still be declared a success, as a score of 60 was counted as being within the Pls' re-calculated "*normal range*" (wrongly understood to mean that participants had "recovered").

The physical function score of 60 used by the Investigators to define the threshold of the "*normal range*" specifically for the PACE Trial contradicts how the authors themselves and their colleagues previously defined the markers of recovery in the same disorder using the same measure -- in 2007 they stated: "**A patient had to score 80 or higher to be considered as recovered**" (Psychotherapy and Psychosomatics 2007;76:171-176) and in 2009 they asserted: "**A cut-off of less than or equal to 65 was considered to reflect severe problems with physical functioning**" (European Journal of Public Health 2009;20:3:251-257). Moreover "*recovery*" is described in the original trial Protocol as a physical function score of 85 or above.

Lord Layard continued: "*There are many studies preceding PACE to show this*" (ie. that people who undergo CBT/GET will always do better than those who have standard medical care); again, this is not true. Simon Wessely himself is on record: "**Even though these interventions appear effective, the evidence is based on a small number of studies and neither approach is remotely curative....These interventions are not the answer to CFS**" (Editorial: Simon Wessely JAMA 19th September 2001;286:11) and "*It should be kept in mind that evidence from randomised controlled trials bears no guarantee for treatment success in routine practice. In fact, many CFS patients, in specialised treatment centres and the wider world, do not benefit from these interventions*" (Huibers and Wessely. Psychological Medicine 2006;36:(7):895-900). The Reno 2009 IACFSME conference was summarised by Professor Charles Lapp, Medical Director of the Hunter-Hopkins Centre, P.A. Charlotte, North Carolina, who recorded: "**Cognitive Behavioural Therapy is not as helpful as once thought**".

Primed by those involved with the PACE trial, Lord Layard began to praise it, saying it was "*a fine piece of work by all normal standards*". He is not qualified to make that assessment. He was not involved with the trial. That statement demonstrates that he is unaware of the many methodological failings that undermine confidence in its findings. It also demonstrates uncritical cronyism.

On the troubled topic of the changes made by the Pls to the protocol, Lord Layard said: "*The changes were made because of discussions affecting the whole research world*". To what is he referring? The changes made were all in one direction, namely to lower the bar for the alleged success of CBT and GET, thereby inflating the numbers for which "recovery" could be claimed.

Lord Layard said: "*What is very interesting is that a separate paper has been written simply on the recovery issue, which uses five or six different criteria of recovery*". What is very interesting is that it took an additional two years after the publishing of selective results in 2011 in The Lancet to produce a contrived success story. If the results were so good, why were they not published in the original paper in The Lancet?

He continued: "*Given the strength of this evidence that we have these treatments which work, it is shocking that they are so little available*"; there is no such "*strength of evidence*": the evidence is that CBT and GET neither reverse nor cure CFS/ME.

Lord Layard said: "*...of course some people get worse during treatment*"; they certainly got worse during the PACE trial, but once the trial was under way, the Pls raised the bar for what they regarded as adverse events (limiting them to death and hospital admission) and removed deterioration during treatment as being an adverse event.

At that point, Lord Layard brought up the favoured topic of alleged vilification of researchers and launched into fulsome praise for Sir Simon Wessely, saying: *“As has already been said, many -- or certainly some -- of the people who work in this area have received repeated insults and even death threats. I pay particular tribute to Sir Simon Wessely at King’s College, London, who has led the field for many years in this area and has stuck to it, despite all this harassment”*. Lord Layard was in full flow when he was stopped by Lord Wallace of Saltaire, who informed Lord Layard that he was over his allotted time. The debate was supposed to be about the effects of the PACE trial on patients with CFS/ME, not a tribute to Sir Simon Wessely, so why was the topic introduced for the second time?

People with CFS/ME are desperate because over the last 25 years many millions of pounds sterling have been allocated to Wessely School psychiatrists and it has been wasted money.

In the US, prominent biomedical researchers are admired and showered with heartfelt gratitude.

5. Baroness Hollins

Lady Hollins spoke after Lord Layard. She made some sensible and valid points, but it was apparent that she had been misinformed on key issues.

She said: *“I have read the research very carefully in preparing my short contribution”*. What research had she read? Is she familiar with the international biomedical evidence-base of over 6,000 peer-reviewed published papers, or had she just read the PACE trial papers?

She continued: *“I agree with the noble Lord, Lord Alderdice, that there is no single cause for this condition”*. Neither Lord Alderdice nor Lady Hollins can know this. Research underway by world-class experts in the US and in Australia may well demonstrate a novel intracellular pathogen as causative. Work on that front is well under way and results are anticipated later this year.

Lady Hollins spoke about the PACE trial “recovery” rates and her own understanding of them, this being that after one year, participants no longer met the criteria for CFS/ME, which she said would be *“heralded as a fantastic outcome for the treatment of MS, Parkinson’s disease or cancer”*. What she appeared to be unaware of is that, despite the Pls’ assertions to the contrary, the criteria used in the PACE trial were not criteria for ME.

As mentioned above, the Pls modified the “London” criteria for ME so that they do not require the cardinal symptom of ME (post-exertional malaise) or the presence of any neurological disturbance for a diagnosis of ME, thus lessening the distinction between true ME and “medically unexplained fatigue” (a somatisation disorder) as captured by the Pls’ own Oxford criteria.

The “London” criteria have never been published in any medical journal and are not on PubMed so are not available for scrutiny or comparison. There is no methods paper which specifically describes them as a case definition; they have never been approved nor have they even been finally defined (there are various versions); despite numerous claims on the internet, it remains uncertain who the authors are or which of the numerous proposed versions is to be preferred. The Pls’ reference cited in The Lancet paper is to the 2004 Westcare Report, which simply said that they were “proposed” criteria.

This means that Professor White was able to (and did) create his own version of the “London” criteria as evidenced on page 188 of the Full Protocol (Professor White’s “version 2” is dated 26.11.2004).

The original intention of the Pls was to use a modified Ramsay definition of ME and this was date-stamped by the MREC as received on 21st March 2003 (<http://www.meactionuk.org.uk/magical-medicine.htm>, page 417). That definition, as approved by the MREC, did not require post-exertional malaise but it did require the following: fluctuation of symptoms from day to day or within the day; headaches; giddiness; muscle pain; muscle cramps; muscle twitches; muscle tenderness; muscle weakness; pins and needles; frequency of passing water; blurred vision; double vision; increased

sensitivity of hearing; increased sensitivity to noise; feeling generally awful, and muscle weakness after exercise (this is different from post-exertional malaise).

However, Professor White further amended the modified Ramsay criteria from the one that the MREC had approved and his further amended version of the “London” criteria specifically states that neurological disturbances ***“are not necessary to make the diagnosis”*** and also states that: ***“the usual precipitation by ‘physical or mental exercise’ should be recorded but is not necessary to meet criteria”***.

Put another way, Professor White’s “London” criteria did not require the cardinal feature of ME to be present in his subgroup of patients in a trial that purported to be studying “CFS/ME”. Given that post-exertional fatigability and malaise is the cardinal feature of ME and that without it, the disorder cannot be diagnosed, it defies credibility that the Chief PI did not require it to be present in his PACE trial participants.

However, notwithstanding the clear statement in the Full Protocol that postexertional malaise is not necessary to meet the “London” criteria as used in the PACE trial, the text of The Lancet article states that participants were also assessed by ***“the London criteria for myalgic encephalomyelitis (version 2) requiring postexertional fatigue”*** when, according to Professor White’s own “London” criteria in the Protocol, this was not the case.

This is a significant discrepancy that requires explanation by Professor White, since two such divergent criteria cannot both have been used in the PACE Trial.

Thus, Baroness Hollins’ rejoicing that PACE participants no longer met the criteria for CFS/ME is premature.

She went on to note that the PACE trial follow-up was only for one year and said: *“I hope the Minister will agree with me that it would be very useful for this study to be funded for follow-up for five years”*. This is the known intention of the PIs and they are actively seeking further funding for a longer follow-up, so it appears that she had been briefed to ask for this.

She continued: *“Better outcomes are achieved for all illnesses....when the overall well-being of the patients – biological, psychological and social – is taken into account”*. Indeed so, but in the case of CFS/ME patients, the PIs persistently ignore or dismiss the biological components and focus on the alleged psychosocial components to the absolute exclusion of the biological components, which receive no mention in the PACE documents or articles.

Lady Hollins said: *“That is not to say that there is no physical reason behind the onset of illness, or that physiological effects are not continuing to maintain or modify the disease process”*. Here, Lady Hollins is expressing support for the latest stance adopted by the PIs, who are now saying that it may be triggered by a virus but that its perpetuation is due to *“reversible physiological changes of deconditioning and avoidance of activity”* ie. CFS/ME is maintained by aberrant illness beliefs as there is no underlying pathophysiology, despite the scientific evidence to the contrary. There is a vital difference between “physiological effects” and pathophysiological effects, and Lady Hollins did not distinguish between them.

As a former President of The Royal College of Psychiatrists, perhaps it is unsurprising that Lady Hollins accepts the views of other psychiatrists (especially when they are so prominent) rather than the biomedical evidence that proves them to be wrong about CFS/ME.

Baroness Hollins then made a seriously misleading statement, again one that Professor White repeatedly claims: *“CFS/ME can be classified under both neurological and psychiatric disorders for clinical purposes”*.

Professor White remains unmoved by the taxonomic rules governing the WHO ICD classification: in December 2008 he gave a presentation at a Neurology and Psychiatry Teaching weekend organised

by the British Neuropsychiatry Association at St Anne's College, Oxford. His presentation ("Chronic fatigue syndrome: neurological, psychological, or both?") is summarised in the Handbook that accompanied the meeting, which said: ***"The ICD-10 classification defines CFS within both the neurology chapter and mental health chapters. Myalgic encephalomyelitis, the alternative name for CFS, is classified as a neurological disease (G93.3) (a.k.a. post-viral CFS), whereas neurasthenia (a.k.a. CFS not otherwise specified) is classified with mental health (F48)".***

It cannot be over-emphasised that Professor White is incorrect: the WHO does not classify "CFS" within both the neurology chapter and the mental health chapter. ME (aka CFS) is classified at G93.3, while chronic "fatigue" is classified at F48.0, **and the same disorder cannot be classified in two different places.**

On 23rd January 2004 the WHO confirmed in writing: ***"According to the taxonomic principles governing ICD-10, it is not permitted for the same condition to be classified to more than one rubric".***

The WHO further confirmed that this means that ME (aka CFS) **cannot** be known as or included with neurasthenia or any other mental or behavioural disorder, as it is a distinct nosological disorder.

Whilst not stating that the WHO International Classification of Diseases (ICD-10) classifies it under both neurological and psychiatric disorders (as Professor White repeatedly asserts), Lady Hollins was quite wrong to say that CFS/ME could be classified under both categories for clinical purposes and she misled their Lordships because CFS/ME is a WHO-classified disorder and the UK Department of Health has confirmed in writing that the NHS was mandated to implement ICD-10 on 1st April 1995 (letter reference: TO00000632783).

For clinical purposes, the peer-reviewed research data supports the following organic abnormalities in ME/CFS, with evidence of:

disrupted biology at cell membrane level; **abnormal brain metabolism**; widespread cerebral hypoperfusion; central nervous system immune dysfunction; **central nervous system inflammation and demyelination**; hypomyelination; **a complex, serious multi-system autoimmune disorder** (in Belgium, the disorder has now been placed between MS and lupus); significant neutrophil apoptosis; **a chronically activated immune system** (eg. the CD4:CD8 ratio may be grossly elevated); diminished NK cell activity; hair loss; **abnormal vascular biology, with disrupted endothelial function**; **significantly elevated levels of isoprostanes**; **cardiac insufficiency and that patients are in a form of cardiac failure**; autonomic dysfunction (especially thermoregulation; frequency of micturition with nocturia); labile blood pressure; pooling of blood in the lower limbs; reduced blood volume (with orthostatic tachycardia and orthostatic hypotension); **respiratory dysfunction, with reduced lung function in all parameters tested**; neuroendocrine dysfunction (notably HPA axis dysfunction); **recovery rates for oxygen saturation that are 60% lower than those in normal controls**; **delayed recovery of muscles after exercise** (note: there is no evidence of deconditioning); **a sensitive marker of muscle inflammation**; the size of the adrenal glands is reduced by 50%, with reduced cortisol levels; up to 92% of ME/CFS patients also have irritable bowel syndrome (IBS); **at least 35 abnormal genes (acquired, not hereditary), specifically those that are important in energy metabolism**; **there are more abnormal genes in ME/CFS than there are in cancer**; **serious cognitive impairment (worse than occurs in AIDS dementia)**; **adverse reactions to medicinal drugs, especially those acting on the CNS**; symptoms fluctuating from day to day and even from hour to hour. There is no evidence that ME/CFS is a psychiatric or behavioural disorder.

For individual references, see: (i) www.meactionuk.org.uk/Organic_evidence_for_Gibson.htm and (ii) www.meactionuk.org.uk/What_the_Experts_say_about_ME.htm).

As Dr Eleanor Stein, Clinical Assistant Professor, Department of Psychiatry, University of Calgary, says: ***"Despite thousands of peer-reviewed papers documenting their unique characteristics and pathophysiology, ME and FM (fibromyalgia) continue to be mistaken for psychiatric conditions. This is problematic because it can delay accurate diagnosis and appropriate treatment, often for years".*** (Psychiatric Times 2013:30:1:1-7).

As a former President of The Royal College of Psychiatrists, one might hope that Baroness Hollins would keep herself informed as to what constitutes a psychiatric disorder and what does not.

6. Baroness Wheeler

Lady Wheeler began by saying that she was not new to this disease but what was new to her was the focus on the PACE trial and *“the opportunity to hear from our expert medical and psychiatrist colleagues about the wider issues and perspectives, and about the trial itself: what it covered, who was involved, its findings and results and the wider, extensive research that is currently being undertaken across the world”*. Unfortunately, nothing in the debate provided the answers, since no mention was made by speakers other than Lady Mar of the *“wider, extensive research”* that disproves the Pls’ psychosocial model of CFS/ME.

Lady Wheeler then said: *“As we have heard, the PACE trial was the largest-ever randomised controlled trial of treatments of CFS/ME”*; once again, their Lordships were misled, because the PACE trial was not a controlled trial.

She continued: *“The patients were recruited from hospital clinics in England and Scotland”*; again this is misleading. The Pls had enormous difficulty in recruiting sufficient participants so, as noted above, on 14th July 2006 the Chief PI sought permission from the West Midlands MREC to recruit participants directly from primary care and accordingly wrote to GPs: *“If you have a patient with definite or probable CFS/ME, whose main complaint is fatigue (or a synonym), please consider referring them to one of the PACE Trial centres”*.

Baroness Wheeler said: *“The trial was not designed to test treatments in patients with severely disabling illness”*; that is true, yet the outcome is being promoted for everyone with a diagnosis of CFS/ME, including the severely affected. The press release on 17th February 2011 to mark the launch of The Lancet article was specific:

Professor Derick Wade from Oxford said: ***“The trial design of this study was very good, and means the conclusions drawn can be drawn with confidence. This is a very significant finding....The study suggests that everyone with the condition should be offered the treatment, and every patient who wishes to be helped should be willing to try one or both of the treatments”***.

The implication of this is that if people refuse to take part in these “rehabilitation” programmes, they do not wish to get better, so they can expect their State benefits to be withdrawn. Professor Wade has written to the DWP advising that, despite the WHO classification, ME/CFS is not a neurological disorder but a ***“non-medical illness”*** (letter dated 22nd August 2005 to Dr Roger Thomas, Senior Medical Policy Advisor in the Benefit Strategy Directorate at the DWP). He has also written to a CFS/ME patient: ***“it is wrong to fit ME/CFS into a biomedical model of illness”*** (letter dated 7th July 2006).

Lady Wheeler continued: *“In fact all the treatments were found to be safe without any serious reactions to treatments in any of the treatment groups”*. The PACE trial did not prove that CBT/GET are safe for people with true ME. Furthermore, the Pls changed their definition of what constituted an adverse event (so a participant might now be house-or-bed-bound and have deteriorated significantly, but this would not be regarded or reported as a serious reaction).

Importantly, the Pls failed to perform serial post-exercise testing on any parameter known to be adversely affected by exercise in CFS/ME patients (for example, lung function tests; cardiovascular tests; tests of oxidative stress to see if exercise has increased levels of harmful free radicals in the blood, including isoprostanes which may increase the risk of a heart attack, which have been clearly demonstrated to be raised in CFS/ME patients: there is compelling evidence from vascular medicine scientists that people with CFS/ME are at increased cardiovascular risk; excreted urinary markers of muscle inflammation; delayed muscle recovery; oxygen saturation levels; immunological tests to see

if cytokine levels were adversely affected, which the Chief PI knows from his own studies is the case, especially the inflammatory cytokines (see above), or cerebral hypoperfusion, hence the PACE PIs cannot claim their interventions are safe because they do not know this as they have not carried out objective post-exercise testing.

This has huge legal implications for health authorities, and this has been recognised by the medical defence unions, who have warned their members that the same care must be taken over prescribing CBT/GET as is taken over prescribing drugs.

Baroness Wheeler said: *“On the NICE guidelines, I support noble Lords who stress that the key issue about them is making sure that they are actually implemented, so that patients can receive effective treatment and care wherever they may live in the UK”*. This statement shows that Lady Wheeler is unaware that the type of supportive CBT recommended in the NICE Guideline differs from the type of directive CBT used in the PACE trial, so the PACE trial cannot be used to corroborate the NICE Guideline.

In fact, all the speakers after Lady Mar appeared unaware of the difference between supportive CBT and directive CBT, even though the directive nature of the PIs’ interventions was clearly set out in The Lancet article. Without understanding this, the premise upon which the PACE trial is based has not been understood, no matter how carefully speakers claim to have read the articles.

Lady Wheeler finished by referring to the new clinical commissioning groups (CCGs) and asking the Minister if she: *“can reassure us that this guidance will include ensuring that guided (sic) exercise training is provided by qualified and trained specialist therapists?”*. Several speakers asked for more access to CBT/GET, so the debate was overtly being used to promote the wishes of the Wessely School psychiatrists even though these interventions are contra-indicated for patients with true ME.

7. The acting Minister, Baroness Northover

The acting Minister then responded. Given that she was a last-minute stand-in, she demonstrated a commendable grasp of the problem when she said: *“We want to see people with CFS/ME being listened to when it comes to decisions about what type of treatment and care may best meet their individual needs”*.

The Minister was correct in stating: *“There is controversy, disagreement and divided and often polarised opinion about its causes and the best way to treat it. The kind of issues raised by the noble Countess today have surrounded the debate for many years. We have seen how passionate but how often opposed are those seeking to address these problems in the debate this afternoon”*, and it is encouraging to hear that the present Government recognises the degree of polarity about CFS/ME.

The Minister was, however, misled by Lord Winston when she said that he *“made clear how extensive”* the world wide research is into the disorder; he did not do so: his analysis of the PubMed entries was not correct and he focused only on the psychosocial researchers, paying no heed at all to the extensive international biomedical research.

It is also troubling that she said: *“We do not yet know...whether it is a disease; a condition, as the noble Baroness, Lady Hollins, described it; or a syndrome, as the noble Baroness, Lady Meacher, described it”*. That is an erroneous statement: ME has been classified since 1969 as a discrete neurological disorder ie. it is a neurological disease.

The present confusion has arisen because those involved with the PACE trial have sought for 20 years to “eradicate” ME (Eradicating “Myalgic Encephalomyelitis”. Pfizer/Invicta: 4-5 /LINC UP, 15th April 1992, Belfast Castle) by subsuming it within their construct of “unexplained chronic fatigue”, to which they refer as CFS/ME, with their stated intention of dropping the “ME” when they deem it expedient (BMJ 2003;326:595-597) and then to reclassify “CFS” as a behavioural disorder under syndromes of chronic “fatigue” under Mental and Behavioural Disorders at ICD-10 F48.0.

It is encouraging that Minister acknowledged that CBT and GET are *“the only treatments that seem to have shown any benefit in clinical trials”*.

The Minister was, regrettably, mistaken when she said *“The decision to fund this trial was based on the MRC’s usual rigorous peer review process for clinical trials”*. Despite innumerable requests and petitions (including requests from the oldest ME charity in the UK) that the PACE trial should not be funded and that it should not go ahead (all of which were ignored), the MRC used peer-reviewers who shared the Wessely School’s beliefs about the nature of CFS/ME and the process was not rigorous at all because the extensive and significant biomedical evidence-base was ignored. Most of the people on the relevant MRC Board (of which Wessely himself had been a member) shared his belief that CFS/ME is a behavioural disorder.

A key tenet of clinical research is that it should build on the foundations of existing knowledge about the disorder being studied, but the MRC allowed the PACE PIs to proceed as if this substantive body of mainstream knowledge did not exist, which was intellectually dishonest. It was also in clear breach of the Declaration of Helsinki (section B11).

During the time when the MRC Research Advisory Group was considering the direction of future research into CFS/ME and how money should be allocated, Simon Wessely was a member of three MRC Boards: the Health Services and Public Health Research Board, the Neurosciences and Mental Health Group and the Monitoring and Evaluating Group.

The report published on 1st May 2003 on the MRC’s CFS/ME Research Strategy advised against any research into aetiology: *“studies investigating potential causal pathways...may not have the same immediate impact on increasing understanding of CFS/ME”* and recommended *“Randomised controlled trials...to evaluate interventions which have been shown in one or more trials to have a benefit”*, ie. trials of CBT/GET). The MRC report was unambiguous: it said that the MRC’s Research Advisory Group did not consider the totality of the evidence and it intentionally did not consider the international biomedical evidence, but it had *“chosen instead to consider how the evidence-base for potentially effective management options can be strengthened....Two specific strategies were identified...for CFS/ME, graded exercise therapy (GET) and cognitive behavioural therapy (CBT)”*.

Also during that consultation period (2002 -2003) the following individuals were appointed to MRC Boards to act *“as a core of scientific advisors, assessing applications to the MRC”*: Dr (now Professor) Trudie Chalder (who became one of the PACE trial PIs); Dr Anthony Cleare; Professor Anthony David; Dr (now Professor) Michael Sharpe (who also became one of the PACE PIs) and Dr (now Professor) Peter White (the PACE trial Chief PI). All these people are known for their strong belief that CFS/ME is a behavioural disorder. At the time, the ME Association posted the following: *“‘Insider trading’ is a criminal offence in Finance incurring unlimited fines and custodial sentencing, and it is surely time and even more important to apply the same or similar regulations and penalties for its equivalent in the field of Medicine and Public Health”*.

In 2005, the MRC’s Neurosciences and Mental Health Board’s Strategy and Portfolio Overview Group produced a portfolio in mental health research which stated: *“Mental health research in this instance covers...CFS/ME”*. This was in defiance of the WHO classification and of the mandate that the NHS must observe the WHO classification.

Hence, it is incorrect for the Minister to be misled into accepting that the MRC’s peer-review process in matters pertaining to CFS/ME are *“rigorous”* because they were nothing of the sort.

This is also the reason why it is misleading for the Minister to say *“The experts who reviewed the application were satisfied that the design put forward was of high quality, would provide useful evidence ... and would help inform doctors on the provision of treatment by the NHS”*. Those “experts” who were in control of funding were the very people who had vested interests in pursuing their own ideology.

The Minister was again misled when she referred to the PACE trial as a controlled trial; as pointed out above, it was not a controlled trial. This is how a lie becomes a fact.

The Minister referred to *"The independent members of the trial steering committee"* having approved the *"plans for secondary analysis"* but again, they were not independent; they included the PIs themselves, the trial statisticians (including Dr Tony Johnson referred to above) and Professor Tom Sensky (also referred to above). The Trial Management Group included the three PIs themselves and Professor Simon Wessely.

The Minister mentioned the issue of secondary analysis, which has been addressed above.

Referring to Lady Mar's concerns about the PACE trial articles, the Minister said: *"As for all MRC funded studies, it is the responsibility of the investigators and the relevant journals, guided by peer-reviewers, to determine how findings are published and when"*. However, despite what the Minister said, the MRC has its own code about publishing when tax-payers' money is involved.

In its Terms and Conditions relating to its grants, MRC-funded authors have a responsibility to report accurately and without obfuscation, and the MRC requires grant-holders to adhere to its policy on data-sharing which is built on the OECD report *"Promoting Access to Public Research Data for Scientific, Economic and Social Development"*. That report identified that publicly-funded research data are *"a public good, produced in the public interest and should be openly available to the maximum extent possible"*. The MRC specifically states that it expects *"valuable data arising from MRC-funded research to be made available to the scientific community with as few restrictions as possible so as to maximise the value of the data for research and for eventual patient and public benefit"* and that such data *"must be shared in a timely and responsible manner"*. It also states: *"Our data-sharing policy applies to all MRC-funded research"*, and it requires that results from this data-sharing *"should meet the high standards of all MRC research regarding scientific quality, ethical requirements and value for money"*.

The PACE trial started in 2004; selective results were not published until February 2011, and further results on the PIs' definition of *"recovery"* were not published until two years after that (on 1st February 2013), ie. nine years after the trial started. What is so difficult about the data analysis, and does such a delay comply with the MRC Terms and Conditions relating to its grant-holders?

As far as The Lancet is concerned, as with so much of the PACE trial, there is more to the publication of the PACE papers than meets the eye. At the time Professor Hooper's formal complaint was sent to The Lancet about his concerns over the PACE trial articles, Dr Stuart Spencer, The Lancet editor responsible for fast-track publication, confirmed on 21st March 2011 that Professor White wanted them fast-tracked, so The Lancet took what he said in his article on trust.

It appears that The Lancet also took what the accompanying Comment by Bleijenberg and Knoop said (which erroneously claimed a 30% recovery rate for CBT/GET, even though no recovery statistics had been published), as The Lancet has confirmed that Professor White himself had approved that Comment prior to publication.

On 29th March 2011 Dr Stuart Spencer again confirmed this (*verbatim*): *"We have to take it on trust...we don't get the statisticians to go round and check every calculation that's been done, we couldn't afford it...It's not up to (our) statisticians to advise on all the adding up...We have to take things on trust"*. It is therefore understood that the fast-tracked PACE articles did not undergo the usual rigorous scrutiny before publication.

Dr Stuart Spencer had confirmed (on 29th March 2011) that, following Professor Hooper's formal complaint, they would have to go ahead with a re-review of the PACE articles by different reviewers, but said that the editor-in-chief, Dr Richard Horton, had instructed him to contact Professor White and ask him to supply a response to Professor Hooper's complaint, and that Professor White had replied by email saying he was not surprised and that *"We'll deal with it"*. It is understood that, following discussions with Professor White, the editor-in-chief cancelled the promised re-review.

The Minister then said that the Countess of Mar *“asked whether the trial data could be reanalysed. As she will know, there are ethical and legal barriers to releasing data to a member of the public without consent when these data contain medical information that might identify the patient”*. Lady Mar’s request did not involve a member of the public; she pointed out the urgent need for a proper reanalysis by truly independent medical statisticians.

Once again, the Minister had been misinformed when she said: *“the PACE trial tested adaptive pacing therapy, which had not previously been tested in a large trial and which is supported by patient organisations”*. This is not correct, as the following extract (which refers to the ICD “ME/CFS” and not to the psychiatrists’ “CFS/ME”) from Professor Hooper’s complaint to The Lancet shows:

Pacing versus adaptive pacing therapy (APT)

Participants were misled by the PIs in that participants believed they were entering a trial testing the efficacy of pacing; they may thus not have been in a position to give fully informed consent. Since patients with classic ME/CFS quickly work out for themselves that in order to survive they have no alternative but to pace themselves, it does not need a £5 million study to prove that pacing is helpful. Pacing is the application of common sense, not a medical intervention.

All three PIs of the PACE Trial, Professors Peter White, Trudie Chalder and Michael Sharpe, are known to be strongly opposed to pacing and the Chief PI, Professor White, has publicly admitted conflicts of interest about it (BMJ 5th January 2002:324:7; BMJ 19th January 2002:324:131; Postgraduate Medical Journal 2002:78:445-446).

For all three PACE Trial PIs to have known conflicts of interest about one of the interventions supposedly being tested in the PACE Trial and to be publicly known to be strongly opposed to that intervention casts serious doubt on the validity of their finding that pacing does not work.

It is therefore necessary to be aware that Adaptive Pacing Therapy (APT) used in the PACE Trial is very different from pacing as practiced by patients with CFS/ME. APT as used in the PACE Trial is a vehicle for incremental aerobic exercise and involves planning, achieving and sustaining targets. The CBT Therapists’ Manual states about APT: *“Activity is therefore planned”*, which indicates a structured activity regime, and the APT Therapists’ Manual lists other requirements for APT including *“plan set activity in advance”* (so activity must be *“set activity”*, not simply what the patient may be capable of doing at the time); there must be *“activity analysis”*; APT participants must *“constantly review model, diaries and activity”* and there is the requirement to *“involve relatives”*, which is nothing like pacing, ie. “doing what you can when you can”.

The Lancet article seriously misleads readers because the authors state: *“Our results do not support pacing, in the form of APT, as a first-line therapy for chronic fatigue syndrome”*. From his published record, Professor White was never going to support pacing, but it is improper to refer to APT used in the PACE Trial as “pacing”; the two are not the same, and other impeccable research (for example, Professor Leonard Jason et al; AAOHN May 2008:56:5) has found pacing to be beneficial for people with CFS/ME.

This is yet another example of how duplicitous the PACE PIs have been.

The Minister went on to say: *“Various noble Lords have paid tribute to the quality of the research”*; they did, but their comments are without foundation, as the Countess of Mar and the international CFS/ME community are keenly aware.

The Minister then said: *“NICE routinely reviews the need to update its guidance in order to take account of the latest available evidence”*; this does not help those with CFS/ME, as NICE has confirmed that when the Guideline Development Group was compiling the Guideline, it was not in their remit to look at the biomedical evidence.

On 14th March 2011 NICE announced that there would be no review of CG53: even though some stakeholders requested a review on the grounds that the interventions recommended in CG53 should be driven by the scientific biomedical evidence (ie. not the Wessely School’s assumptions of reversibility with cognitive restructuring), NICE remained intransigent: *“...interventions recommended in the original guideline, such as CBT and GET, were described as the interventions for which there is the clearest evidence-base of benefit. This is supported by the recently published PACE trial....The results of the study are in line with current NICE guideline recommendations on the management of*

CFS/ME....There are no factors...which would invalidate or change the direction of the current guideline recommendations. The CFS/ME guideline should not be updated at this time”.

The Minister’s statement that “*The PACE trial was funded to respond to the concerns of patients, carers and doctors that more research into CFS/ME was required*” is an egregious travesty of the truth.

The PACE Trial inhabits a unique and unenviable position in the history of medicine. It is believed to be the first and only clinical trial that patients and the charities that support them tried to stop before a single patient could be recruited.

The ME Association was adamant that the PACE trial should be halted and on 22nd May 2004 posted the following on its website (which was printed in its magazine “ME Essential” in July 2004):

“The MEA calls for an immediate stop to the PACE and FINE trials

*“A number of criticisms concerning the overall value of the PACE trial and the way in which it is going to be carried out have been made by the ME/CFS community. The ME Association believes that many of these criticisms are valid. **We believe that the money being allocated to the PACE trial is a scandalous way of prioritising the very limited research funding that the MRC have decided to make available for ME/CFS, especially when no money whatsoever has so far been awarded for research into the underlying physical cause of the illness. We therefore believe that work on this trial should be brought to an immediate close and that the money should be held in reserve for research that is likely to be of real benefit to people with ME/CFS.** We share the concerns being expressed relating to informed consent, particularly in relation to patients who are selected to take part in graded exercise therapy. The Chief Medical Officer’s Report (section 4.4.2.1) noted that 50% of ME/CFS patients reported that graded exercise therapy had made their condition worse, and we therefore believe that anyone volunteering to undertake graded exercise therapy must be made aware of these findings”.*

In its magazine “ME Essential” (February 2005), the ME Association’s Medical Advisor wrote: ***“Now some bad news. The MRC made it clear that priority should be given to funding further behavioural interventions. The ME Association believes that the MRC research strategy is seriously flawed and has called for money to be spent on looking at the underlying physical causes of ME/CFS”.***

It is thus completely wrong for the Minister to inform their Lordships that the PACE trial was funded to respond to the concerns of patients, their carers and doctors.

Overall, there were many significant inaccuracies spoken in the debate, which can only result in further harm to people with CFS/ME and in their justified perception that they have been abandoned by the agencies of State that are charged with helping and protecting them.

An illustration of this is the lack of insight exemplified by Lord Winston in his comments in the Mail on Sunday on 10th February 2013 (just four days after the PACE debate), where he said about the situation at Stafford Hospital that resulted in so many unnecessary deaths:

“The callous and inhumane treatment meted out to the ill and vulnerable was nothing short of disgraceful: a damning indictment of the pervasive loss of compassion and dedication among some in a caring profession that was once the envy of the world.

“As a trainee, whilst I worked in some excellent hospitals, some were appalling. In one, I argued with a distinguished consultant with a God-like attitude who ignored published evidence because he ‘knew better’.

“What has been forgotten is that a valued workforce values patients. And if patients are valued then thousands will not die unnecessarily”.

From the PACE debate, it is clear that Lord Winston himself has become the God-like consultant who ignored published evidence because he “knew better”.

The published evidence is that patients die from CFS/ME but they do not die from chronic fatigue.

Cardiovascular dysfunction in ME/CFS patients has been well documented for many years. As long ago as 1957, Dr Andrew Wallis recorded *“myocarditis, with dyspnoea on slightest exertion”*. Professor Peter Behan wrote in 1988 that *“evidence of cardiac involvement may be seen”*, and Dr Jay Goldstein noted in 1990 that *“a significant group have cardiac symptoms”*. An important study by Professor Benjamin Natelson and Dr Arnold Peckerman published in 2003 **demonstrated that there might be periods in daily activities when demands for blood flow are not adequately met, compromising metabolic processes, including the possibility of under-perfusion in the kidneys and gut.**

Evidence and illustrations of cardiovascular dysfunction in ME/CFS

- ***“The blood vessels throughout the nervous system were distended with red blood cells ... the most characteristic change was infiltration of the blood vessel walls”***
- *“ME is a multisystem syndrome including nervous, cardiovascular, endocrine and other involvement. Vasculitic skin lesions, autonomic dysfunction, especially circulation and thermoregulation”*
- ***“These chronic ME/CFS patients complain of severe chest pain and shortness of breath as if suddenly stopped by an invisible barrier”***
- *“Evidence of cardiac involvement may be seen: palpitations, severe tachycardia with multiple ectopic beats and occasional dyspnoea may occur and are quite distressing. It is of great interest that some patients have evidence of myocarditis”*
- ***“There is a high incidence of cardiomyopathy in CFS patients”***
- ***“Convincing evidence of cardiovascular impairment can be demonstrated”***
- *“As a group, the ME/CFS patients demonstrated significantly lower cardiovascular as well as ventilatory values compared with the control group. **These results indicate either cardiac or peripheral insufficiency embedded in the pathology of ME/CFS**”*
- *“Several groups have shown that ME/CFS patients have abnormal regulation of heart rate and blood pressure, as well as high rates of allergic disease”*
- *“Many people with ME/CFS may have a serious heart problem. When you exercise, your heart pumps out more blood. But these patients’ hearts actually pump less blood”*
- ***Without exception, every disabled CFIDS (ie ME/CFS) patient is in heart failure***
- *“Q” stands for cardiac output in litres per minute. In ME/CFS patients, Q values correlated – with great precision – with the level of disability. **When disabled ME/CFS patients stand up, they are on the edge of organ failure due to extremely low cardiac output as their Q drops to 3.7 litres per minute (a 50% drop from the normal of 7 litres per minute)***
- ***“All disabled ME/CFS patients, all of whom have post-exertional fatigue, have low Q and are in heart failure”***

- In order to improve cardiac output in ME/CFS, patients need to lie down, as this increases the cardiac output by 2 litres per minute. Some ME/CFS patients need to lie down all the time to augment their blood volume in order to survive
- **Aerobic exercise may kill the patient with ME/CFS. There is an objective database in key medical literature that includes evidence of diastolic dysfunction and heart failure in ME/CFS**
- ME/CFS is a compensatory response to down-regulate energy production and oxygen transport in order to reduce tissue damage. Attempts to push beyond energy limits will cause injury
- **Diastolic failure begins when the body can no longer compensate and there is a reduction in cardiac output. This is seen in 80% of ME/CFS patients**
- **In order to stay relatively stable, it is essential for the ME/CFS patient not to create metabolic demand that the low cardiac output cannot match**
- **Graded exercise therapy is ill-advised – if a patient has abnormal oxygen consumption, muscles will not have enough oxygen and exercise will result in relapse**
- **The cardiac index of ME/CFS patients is so severe that it falls between the value of patients with myocardial infarction (heart attack) and those in shock.**

From a moral perspective alone, how can the UK Government even consider funding further trials of CBT and graded aerobic exercise when such exercise may well kill participants with true ME as opposed to chronic “fatigue”?

Apart from the Countess of Mar, by praising and supporting the PACE trial, speakers in the House of Lords debate may have been putting countless ME patients at substantial risk, including risk of death.

Their Lordships will know that ignorance is no defence in law.