MAGICAL MEDICINE:
HOW TO MAKE A DISEASE DISAPPEAR

Background to, consideration of, and quotations from the Manuals for the Medical Research Council's PACE Trial of behavioural interventions for Chronic Fatigue Syndrome / Myalgic Encephalomyelitis, together with evidence that such interventions are unlikely to be effective and may even be contra-indicated

> ***"the belief that ME/CFS is a psychological illness is the error of our time".*** (The Complexities of Diagnosis. Byron Hyde. In: Handbook of Chronic Fatigue Syndrome. Ed: Leonard A Jason et al. John Wiley & Sons Inc. 2003)

> ***"…to assign someone to the wrong category on the basis of a false understanding of the nature of the illness and its context is an example of a well-known phenomenon which psychologists term 'fundamental attribution error' "*** (Dr Derek Pheby: InterAction 2009:69:16-17)

> ***"Does (XMRV) prove once and for all that ME/CFS is not a psychological or psychosomatic illness as described by those who don't understand the disease? Absolutely! Actually there are thousands of research articles showing the very real biological problems that ME/CFS patients experience. Only the most stubborn and misinformed individuals refuse to believe that this disease is real and serious"*** (Whittemore Peterson Institute for Neuro-Immune Disease, October 2009. http://wpinstitute.org/xmrv/xmrv_qa.html)

> ***"Scientists could be on the brink of a breakthrough. That would – at least – go some way to compensating for the shameful manner in which sufferers were treated for so long by the medical profession"*** (Leading Article; Independent, 9th October 2009)

> ***"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 (in 2009) I would rather have HIV"*** (Nancy Klimas, one of the world's foremost AIDS and ME/CFS physicians; Professor of Medicine and Immunology, University of Miami; New York Times, 15th October 2009)

Malcolm Hooper

With contributions from members of the ME Community
Researched by Margaret Williams

Contact address: malcolm.hooper@virgin.net
Malcolm Hooper
Emeritus Professor of Medicinal Chemistry
Department of Life Sciences
University of Sunderland
SR2 7EE, UK.

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EXECUTIVE SUMMARY

The Medical Research Council's PACE Trial of behavioural interventions for Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (CFS/ME) attracted considerable opposition from the outset and the Principal Investigators had difficulty in recruiting a sufficient number of participants. PACE is the acronym for **P**acing, **A**ctivity, and **C**ognitive behavioural therapy, a randomised **E**valuation, interventions that, according to one of the Principal Investigators, are without theoretical foundation.

The MRC's PACE Trial seemingly 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 have tried to stop before a single patient could be recruited and is the only clinical trial that the Department for Work and Pensions (DWP) has ever funded.

Since 1993, the giant US permanent health insurance company UNUMProvident has been advising the UK DWP about the most effective ways of curtailing sickness benefit payments. The PACE Trial is run by psychiatrists of the Wessely School, most of whom work for the medical and permanent health insurance industry, including UNUMProvident. These psychiatrists insist – in defiance of both the World Health Organisation and the significant biomedical evidence about the nature of it -- that "CFS/ME" is a behavioural disorder, into which they have subsumed ME, a classified neurological disorder whose separate existence they deny. Their beliefs have been repudiated in writing by the World Health Organisation.

In 1992, the Wessely School gave directions that in ME/CFS, the first duty of the doctor is to avoid legitimisation of symptoms; in 1994, ME was described as merely "a belief"; in 1996 recommendations were made that no investigations should be performed to confirm the diagnosis and in 1999 patients with ME/CFS were referred to as "the undeserving sick".

There are legitimate concerns about the MRC PACE Trial that are centred on apparent coercion, exploitation of patients, contempt in which patients are held, manipulation, pretension, misrepresentation, flawed studies yielding meaningless results and lack of scientific rigour; the unusual personal financial interest of the Chief Investigator; the vested interests of the Principal Investigators; high rates of Severe Adverse Events (SAEs) and in particular, the underlying non-clinical purpose of the trial, which seems to have the politically generated aim of removing patients from benefits (ie. the use of motivational behaviour therapy to achieve the intended result of the cessation of benefits for patients with "CFS/ME"). The Manuals used in the Trial seem to show that the authors either ignore medical science or they do not understand medical science.

There is rightful objection to the denial of appropriate investigations and to the nationwide implementation of behavioural modification as the sole management strategy for the nosological disorder ME/CFS. That strategy is believed to be based on (i) the commercial interests of the medical and permanent health insurance industry for which many members of the Wessely School work and (ii) the dissemination of misinformation about ME/CFS by the Wessely School, whose members also act as advisors to UK Government agencies including the DWP, which it is understood has specifically targeted "CFS/ME" as a disorder for which certain State benefits should not be available.

The Wessely School rejects the significant body of biomedical evidence demonstrating that chronic "fatigue" or "tiredness" is not the same as the physiological exhaustion seen in ME/CFS and persists in believing that they have the right to demand a level of "evidence-based" definitive proof that ME/CFS is not an *"aberrant belief"* as they assert, when their biopsychosocial model of "CFS/ME" that perpetuates their own aberrant belief about the nature of ME/CFS has been exposed by other psychiatrists as being nothing but a myth.

There are some extremely disquieting issues surrounding the MRC PACE Trial and documents obtained under the Freedom of Information Act allow the full story to be told for the first time.

MYALGIC ENCEPHALOMYELITIS/CHRONIC FATIGUE SYNDROME

A review of biomedical clinical and research literature 1955-2006

(Substantial extracts from Prof. Malcolm Hooper's submission to UK Parliamentary Inquiry, 2005)

ME/CFS Society of Western Australia

Facts:

Myalgic Encephalomyelitis (ME) has been classified as a disorder of the central nervous system since 1969 – (World Health Organization International Classification of Diseases) WHO ICD 10 G 93.3

The renaming of ME to Chronic Fatigue Syndrome (CFS) in 1988, giving misplaced emphasis to "fatigue", trivializes the substantial disability of the disease 1 – which can extend to the wheelchair or bed-bound requiring 24 hour care

ME/CFS is characterized by neurological, immunological, gastrointestinal, cardiovascular and musculoskeletal features – severe forms can present with paresis, seizures, intractable savage headaches and life threatening complications

Amorphous definitions and diagnostic symptom criteria have contaminated study cohorts and corrupted research data 2-10 – researchers and clinicians participating in the 2005 Adelaide ME/CFS Research Forum unanimously endorsed the adoption of the acclaimed 2003 Canadian Clinical Criteria

ME/CFS may include clinical syndromes linked to infectious agents and toxic exposures 11-15 – incl. Epstein Barr virus, ciguatoxin 13, organophosphates and organochlorines 12,14

Prevalence estimates are 235-700 per 100,000 affecting all socio-economic and ethnic groups, and men and women of all ages 16-21 – more prevalent than AIDS, lung or breast cancer 19

Disease impact 22-26 – quality of life equivalent to late stage AIDS 17,27, chronic obstructive lung 25,28 and heart disease and end stage renal failure 29

Some experience recovery (average 7yrs 17**), some partially recover and a significant proportion (25%** 20**) are permanently incapacitated** 17-20,22-23

Biomedical Abnormalities:

Immune System, including:

• **chronic immune activation and dysfunction** 24,30-32 evidence of persistent viral infection 33 (enteroviral 34-41, EBV 42-47 and HHV-6/7 43,45-50), activation of the 2-5A anti-viral pathway 47,51-56, low natural killer cells and cytotoxicity 33,47,54,57-63, T-cell abnormalities 59,61-62,64-66, pro-inflammatory cytokines and inflammation 66-72, increased cell apoptosis (death) 73-74 and allergy 54,75-77

• **abnormal immuno-genetic expression** 61,66,78-81

Brain/Central Nervous System, including:

• **objective measurement of dysfunction** 54,82-86 –deficits in working memory, concentration, information processing 87-95, autonomic function 96-98 (incl. neurally mediated hypotension and orthostatic intolerance)

• **abnormalities** –regional brain hypoperfusion 99-106 by SPECT, white and gray matter abnormalities 106-112 by MRI, inflammation 66,106-107,113-114, hypomyelination 83,113-114, neurotransmitter 115-116,119 and metabolic dysfunction 117-121 by MRS/PET and abnormal spinal fluid proteins 122-123

• **abnormal neuro-genetic expression** 114

Endocrine System: impaired activation of the hypothalamic-pituitary-adrenal (HPA) axis 124-131 and abnormalities of neuroendocrine-genetic expression 78

Heart and Circulatory System: hypoperfusion 54,83,99-106,132-136, impaired vascular control 27,134-137 (incl. abnormal response to acetylcholine), low blood volume 134-135, vasculitis 136-137 (incl. raised oxidative stress, inflammation and arterial stiffness 138-139) and heart dysfunction 132,135,140-141

Muscular: structural and biochemical abnormalities 38,68,89,142-148 including impaired muscle recovery after exercise 149-154 (exercise responsive gene expression abnormal, worsening after exercise 155)

Others: gastrointestinal dysfunction 156-158 including food intolerance 159-160 and IBS 156,161, mitochondrial dysfunction 38,82,125,162-163 including abnormal mitochondrial associated gene expression 164 and ion transport channelopathy 155,165-166

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MAGICAL MEDICINE:
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Introduction

The Medical Research Council's PACE Trial of certain "behavioural modification" interventions for patients with Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (CFS/ME) is controversial on many levels. "PACE" is the acronym for "**P**acing, **A**ctivity, and **C**ognitive behaviour therapy; a randomised **E**valuation".

The PACE trial is being conducted under the auspices of the Medical Research Council (MRC) and is funded by the MRC, the Scottish Chief Scientist's Office, the Department of Health (DoH) and the Department for Work and Pensions (DWP). The PACE Trial is the only clinical trial that the DWP has ever funded.

The MRC's PACE Trial seemingly 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 which support them have tried to stop before a single patient could be recruited.

Why would people with a severely disabling disease -- a disease that manifests the pathology summarised on the preceding two pages -- seek to stop research into their own condition?

To answer this question it is necessary to understand the motives of the trial researchers – a group of UK psychiatrists and their adherents who advise that the search for a single identifiable cause is meaningless and whose stated aim is to "eradicate" Myalgic Encephalomyelitis, a disease that has been classified by the World Health Organisation (WHO) in the International Classification of Diseases (ICD) as a neurological disorder for the last 40 years, currently under Disorders of Brain at ICD-10 G93.3 (to which in ICD-10 the WHO specifically codes "chronic fatigue syndrome" (CFS), hence the use of the term ME/CFS to signify the neurological disease ME).

This is a classification with which these psychiatrists disagree. Instead, they believe ME/CFS (which they call "CFS/ME") to be a behavioural disorder that is classified as a "fatigue" syndrome in ICD-10 at F48.0 under Mental and Behavioural Disorders and that it is perpetuated by the "*aberrant beliefs*" of the patients themselves, and they seek to modify such aberrant beliefs using a programme of Cognitive Behavioural Therapy (CBT) designed by themselves, which incorporates aerobic Graded Exercise Therapy (GET).

These psychiatrists and their supporters, many of whom work for the medical and permanent health insurance industry, are known as the "Wessely School" (Hansard: Lords: 9th December 1998:1013), a small but influential group led by Professor Simon Wessely from King's College Hospital and the Institute of Psychiatry (IoP), London, whose intention is said to be to "eradicate" ME (Eradicating "Myalgic Encephalomyelitis". Pfizer/Invicta: 4-5 /LINC UP, 15th April 1992, Belfast Castle) by dropping "ME" from "CFS/ME" when 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.

Indeed, this has already commenced because, using Wessely's own material, in 2000 the first edition of the IoP's "Guide to Mental Health in Primary Care" included "CFS/ME" as a mental disorder. (This Guide was wrongly described by Ministers of State as the "WHO Guide" because as an acknowledged WHO Collaborating Centre on mental health, the IoP is entitled to use the WHO logo). **In September 2001, the WHO issued a statement repudiating the unofficial re-classification by the UK Collaborating Centre at the IoP, saying that it was at variance with the WHO's position.** An erratum to the Guide had to be issued, but only after 30,000 copies had been sold. The matter was raised in Parliament on 22nd January 2004, when Earl Howe noted that Professor Wessely had: *"effectively hijacked the WHO logo to give credence to his own view of ME as a mental illness"* (Hansard: Lords: 23rd January 2004:656:7:1192).

Undaunted, these psychiatrists then asserted that the WHO itself had classified the same disorder in two places in ICD-10, once in the Neurological Section (G93.3) and also in the Mental (Behavioural) Section (F48.0).

Once again, the psychiatrists' claims were repudiated by the WHO, who on 23rd January 2004 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/CFS **cannot** be known as or included with neurasthenia or any other mental or behavioural disorder, as ME/CFS is a distinct nosological disorder.

Wessely, however, does not agree: he believes that ME is a behavioural disorder and that patients' ascription of the disease to a virus is *"somatisation par excellence"* (see below).

It is Professor Wessely who is in charge of the MRC PACE Clinical Trial Unit.

There is a significant amount of documented international concern about the Wessely School's stance and the harm it might do to patients.

Another curious factor about the PACE Trial is the role played by one of the patients' charities (Action for ME), without whose help the PACE Trial might never have happened – see below. It is a Government-funded charity, having received substantial Section 64 funding (Health Services Act 1968) in return for supporting DoH policy priorities (which currently include managing "CFS/ME" as a behavioural disorder).

Good science requires that hypotheses are tested in an objective manner, but there are many disturbing aspects about the MRC PACE Trial.

Given that the Investigators have already formed their belief that "CFS/ME" is a behavioural disorder, it is troubling to observe how they seem to have allowed their beliefs to undermine the objectivity of the trial:

- participants were to be chosen using criteria designed by the Investigators themselves rather than using criteria accepted by the international medical community
- the Investigators' criteria were financially supported by the Chief Investigator himself
- the Investigators abandoned their intention to use any objective measurements of outcome and will define the self-reported outcome measures using a scale devised by themselves (which has been described as "*a parody of modern scientific measurement"* – see below)
- the Investigators have even redefined the meaning of the word "recovery" – see below.

The Investigators have received millions of pounds sterling to carry out this trial, even though they already know the answers and they have publicly acknowledged that for ME/CFS patients their psychotherapy interventions are not remotely curative and that many patients do not benefit from them – see below.

Part of the Trial therapists' training appears to include misleading participants: therapists are told to assure participants they believe their illness is "real" and to show empathy, whilst also being informed in their training that there is no underlying pathology in "CFS/ME", so there is one message for the therapists and another for participants.

Therapists and research nurses must achieve "*positive relationships"* with participants. Research Nurses (RNs) *"will be selected and trained to achieve positive relationships with participants. In addition to seeing them for a minimum of 5 times in 52 weeks, we will use techniques commonly employed in cohort studies to maintain participation"* (Trial Protocol, final version 5.0, 01.02.2006). This involves sending birthday cards to participants in order to create an illusion of "*warmth"* and of "*empathy"* that is intended to elicit positive

associations purely in order to "*maintain participation*", a tactic that may be considered misleading and even a form of coercion.

Participants are trained to ignore their symptoms (which a world expert in the disorder described as "*dangerous*" in his Witness Statement to the High Court – see below).

Not only were patients seemingly coerced into the Trial, but they were also to be subjected to "thought modification" and to engage in incremental aerobic exercise that may at best be of no value and – according to some international experts in the disorder – at worst might kill them.

Fully informed consent may not have been obtained from participants, because the beliefs of the Investigators and the therapists about the disorder were not made explicit to them (ie. that the Investigators consider it to be a behavioural disorder and that the PACE Trial is based on their assumption that participants do not have a physical disease), which takes advantage of participants' lack of knowledge. To take advantage of patients is in breach of the General Medical Council Regulations.

The PACE Trial started in 2004 and aimed to recruit 600 participants. Originally based in three different Centres (King's College, London; St Bartholomew's Hospital, London and the Western General in Edinburgh), three new Centres subsequently began recruiting participants (the John Radcliffe Hospital in Oxford; the Royal Free Hospital in London and a second Centre at St Bartholomew's Hospital, London).

The PACE Trial team produces a Newsletter for participants and in Issue 2, March 2007, the Chief Investigator, Professor Peter White, a psychiatrist from St Bartholomew's Hospital, wrote: "*These extra centres will significantly boost recruitment into the study*".

However, it seems that because of the continued failure to meet the recruitment target, it was deemed necessary to open a seventh Centre at Frenchay Hospital in Bristol, which began recruiting in April 2007.

Participants were to be randomly allocated to one of four groups (Pacing, Activity/Exercise, Cognitive Behavioural Therapy, or Standardised Specialist Medical Care) with the objective of achieving four groups of 150 patients from – according to the 2002 Chief Medical Officer's Working Group Report on "CFS/ME" -- 240,000 sufferers in the UK. No severely affected patient and no children were to be included in the trial.

Despite such a relatively small number in each arm of the trial, using the trial's leitmotif of *"positive reinforcement"*, the PACE Participants' Newsletter, Issue 3, December 2008 states: "*The PACE trial retains a significant role as the largest trial ever for comparison of rehabilitative therapies for CFS/ME*".

The results are due to be published in 2010, originally said to be summer, then autumn, but – according to the Chief Investigator – now moved forward to the spring.

There are some extremely disquieting issues surrounding the MRC PACE Trial, and documents obtained under the Freedom of Information Act allow the full story to be told for the first time.

The PACE Trial: source of information

The PACE Trial Manuals, as well as Minutes of meetings and related correspondence (amounting to approximately 2,000 pages) were obtained via the Freedom of Information Act (FOIA). Requests were made to various bodies including the MRC, the Department for Work and Pensions and the Scottish Chief Scientist's Office and took over twelve months to achieve.

There are three PACE Trial Manuals for therapists (relating to Cognitive Behaviour Therapy, Graded Exercise Therapy, and Adaptive Pacing Therapy [APT] respectively) and one for doctors (relating to

Standardised Specialist Medical Care or "SSMC"); apart from the latter, there are also respective versions for participants.

It is notable that the West Midlands Multicentre Research Ethics Committee's letter of 29th October 2002 confirming approval of Peter White's application for ethical approval states: *"MREC noted the importance of the study and wished to commend the researchers on the RCT design"* (random controlled trial), an unusual commendation which seems to show bias from the outset and may indicate the MREC's ignorance of the issues that lie at the heart of the international disquiet surrounding the MRC PACE Trial.

Every effort has been made to view objectively the PACE Trial information that informs these comments. However, the information must be assessed in the light of the significant body of evidence that ME/CFS is not a behavioural disorder; moreover the quotations from the Manuals speak for themselves.

Although every Manual states that it is copyright and that no part may be reproduced without permission, the Information Commissioner's Office has confirmed that if documents are released under the Freedom of Information Act, they enter the public domain and can be used by members of the public and not only by the person who made the application.

It is the case that the MRC was not happy that so much of what it regarded as confidential information about the PACE Trial has been released. A letter dated 14th February 2008 from the Information Commissioner's Office to the person who made the FOIA application states: *"The MRC has expressed its concern over how you came to be in possession (of this information)".*

Given the nature of that information, the MRC's concern may well be justified.

The difference between ME/CFS and "CFS/ME"

What the Wessely School refers to "CFS/ME" is, according to them, a condition of "medically unexplained" fatigue that is perpetuated by inappropriate illness beliefs, pervasive inactivity, current membership of a self-help group and being in receipt of disability benefits (PACE Trial Identifier, section 3.9) and it should be managed by behavioural interventions (CBT and GET). Simon Wessely believes that it is the same as neurasthenia: "*Neurasthenia would readily suffice for ME"* (Lancet 1993:342:1247-1248) and that attribution by patients to a virus is somatisation "*par excellence"* (J Psychosom Res 1994:38:2:89-98). The Wessely School believes that there are no physical signs of disease and assert that there is no pathology causing the patients' symptoms, simply that patients are "*hypervigilant*" to "*normal bodily sensations"* (see below).

Seemingly because of the Wessely School's beliefs, children with ME/CFS have been diagnosed as having "pervasive refusal syndrome" and many have been forcibly removed from their distraught parents (see below), who themselves have been labelled as having Munchausen's Syndrome by Proxy, a damaging label that is never deleted from their medical records.

Whilst Wessely School psychiatrists continue to believe and teach (and advise Government agencies) that "CFS/ME" is a behavioural disorder that must be managed by behavioural interventions and incremental aerobic exercise (and which two of the PIs assert can be "cured" by those interventions), in reality true ME/CFS affects every system in the body and many physiological abnormalities have been documented.

At the Press Briefing held on 3rd November 2006 by the US Centres for Disease Control to announce its ME/CFS awareness campaign, two eminent professors who specialise in ME/CFS spoke on public record about the nature of ME/CFS. 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…(and) they change a person's life.

"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, Professor of Medicine and Immunology at the University of Miami (who at the time was President of the International Association for Chronic Fatigue Syndrome, an organisation of medical professionals and research scientists), said:

"I've been waiting for this day for a long time. Over the past 20 years, I've treated more than 2,000 (ME)CFS patients.

"Whilst attitudes have improved in recent years, the launch of this national awareness campaign is so important to increasing understanding of this illness.

"Historically, it's been the lack of credibility in this illness that has been one of our major stumbling blocks to making progress.

"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.

"*The CFS toolkit should be in the hands of every doctor…in the country, because this is the key to moving forward*" (http://www.cdc.gov/media/transcripts/t061103.htm).

Referenced illustrations from the medical literature are provided in Section 2, but an introductory overview of documented abnormalities in ME/CFS include the following:

- abnormalities of the central nervous system include abnormalities of brain cognition, brain perfusion, brain metabolism and brain chemistry; there is evidence of low blood flow in multiple areas of the brain; neuro-imaging has revealed lesions in the brain of approximately 80% of those tested and according to the researchers, these lesions are probably caused by inflammation: there is a correlation between the areas involved and the symptoms experienced; abnormalities on SPECT scans provide objective evidence of central nervous system (CNS) dysfunction; there is evidence of a chronic inflammatory process of the CNS, with oedema or demyelination in 78% of patients tested; there is evidence of a significant and irreversible reduction in grey matter volume (especially in Brodmann's area 9) which is related to physical impairment and may indicate major trauma to the brain (which could also explain the low recovery rate); there is evidence of seizures; a positive Romberg is frequently seen in authentic ME/CFS patients

- abnormalities of the autonomic and peripheral nervous systems: there is evidence of dysautonomia in ME/CFS patients

- cardiovascular dysfunction: there is evidence of haemodynamic instability and aberrations of cardiovascular reactivity (an expression of autonomic function); there is evidence of diastolic cardiomyopathy; there is evidence of endothelial dysfunction; there is evidence of peripheral vascular dysfunction with low oxygenation levels and poor perfusion and pulsatilities; there is evidence of abnormal heart rate variability and evidence of abnormal orthostasis; there is evidence of abnormally inverted T-waves and of a shortened QT interval, with electrophysiological aberrancy; there is evidence of abnormal oscillating T-waves and of abnormal cardiac wall motion (at rest and on stress); there are indications of dilatation of the left ventricle and of segmental wall motion abnormalities; there is evidence that the left ventricle ejection fraction – at rest and with exercise – is as low as 30%; there is evidence of reduced stroke volume

- respiratory system dysfunction: there is evidence of significant reduction in many lung function parameters including a significant decrease in vital capacity; there is evidence of bronchial hyper-responsiveness

- a disrupted immune system: there is evidence of an unusual and inappropriate immune response: there is evidence of very low levels of NK cell cytotoxicity; there is evidence of low levels of autoantibodies (especially antinuclear and smooth muscle); there is evidence of abnormalities of immunoglobulins, especially sIgA and IgG_3, (the latter having a known linkage with gastrointestinal tract disorders); there is evidence of circulating immune complexes; there is evidence of a Th1 to Th2 cytokine shift; there is evidence of abnormally diminished levels of intracellular perforin; there is evidence of abnormal levels of interferons and interleukins; there is evidence of increased white blood cell apoptosis, and there is evidence of the indisputable existence of allergies and hypersensitivities and positive mast cells, among many other anomalies, with an adverse reaction to pharmacological substances being virtually pathognomonic

- virological abnormalities: there is evidence of persistent enterovirus RNA in ME/CFS patients; there is evidence of abnormalities in the 2-5 synthetase / RNase L antiviral pathway, with novel evidence of a 37 kDa binding protein not reported in healthy subjects or in other diseases; there is evidence of reverse transcriptase, an enzyme produced by retrovirus activity, with retroviruses being the most powerful producers of interferon; there is evidence of the presence of HHV-6, HHV-8, EBV, CMV, Mycoplasma species, Chlamydia species and Coxsackie virus in the spinal fluid of some ME/CFS patients, the authors commenting that it was surprising to find such a high yield of infectious agents on cell free specimens of spinal fluid that had not been centrifuged; recently a direct link between a gammaretrovirus (XMRV, which is the same family as the AIDS virus) and ME/CFS has been demonstrated

- evidence of muscle pathology: this includes laboratory evidence of delayed muscle recovery from fatiguing exercise and evidence of damage to muscle tissue; there is evidence of impaired aerobic muscle metabolism; there is evidence of impaired oxygen delivery to muscle, with recovery rates for oxygen saturation being 60% lower than in normal controls; there is evidence of prolonged EMG jitter in 80% of ME/CFS patients tested; there is evidence of greater utilisation of energy stores; there is evidence that total body potassium (TBK) is significantly lower in ME/CFS patients (and abnormal potassium handling by muscle in the context of low overall body potassium may contribute to muscle fatigue in ME/CFS); there is evidence that creatine (a sensitive marker of muscle inflammation) is excreted in significant amounts in the urine of ME/CFS patients, as well as choline and glycine; there is evidence of type II fibre predominance, of scattered muscle fibre necrosis and of mitochondrial abnormalities

- neuroendocrine abnormalities: there is evidence of HPA axis dysfunction, with all the concomitant implications; there is evidence of abnormality of adrenal function, with the size of the glands being reduced by 50% in some cases; there is evidence of low pancreatic exocrine function; there is evidence of an abnormal response to buspirone challenge, with a significant increase in prolactin

release that is not found in healthy controls or in depressives; there is evidence of abnormal arginine – vasopressin release during standard water-loading test; there is evidence of a profound loss of growth hormone; even when the patient is euthyroid on basic screening, there may be thyroid antibodies and evidence of failure to convert T4 (thyroxine) to T3 (tri-iodothyronine), which in turn is dependant upon the liver enzymes glutathione peroxidase and iodothyronine deiodinase, which are dependant upon adequate selenium in the form of selenocysteine (which may be inactivated by environmental toxins)

- defects in gene expression profiling: there is evidence of reproducible alterations in gene regulation, with an expression profile grouped according to immune, neuronal, mitochondrial and other functions, the neuronal component being associated with CNS hypomyelination

- abnormalities in HLA antigen expression: Teraski from UCLA found evidence that 46% of ME/CFS patients tested were HLA-DR4 positive, suggesting an antigen presentation

- disturbances in oxidative stress levels: there is mounting evidence that oxidative stress and lipid peroxidation contribute to the disease process in ME/CFS: circulating in the bloodstream are free radicals which if not neutralised can cause damage to the cells of the body, a process called oxidative stress: in ME/CFS there is evidence of increased oxidative stress and of a novel finding of increased isoprostanes not seen in any other disorder; these raised levels of isoprostanes precisely correlate with patients' symptoms (isoprostanes being abnormal prostaglandin metabolites that are highly noxious by-products of the abnormal cell membrane metabolism); there is evidence that incremental exercise challenge (as in graded exercise regimes) induces a prolonged and accentuated oxidative stress; there is evidence of low GSH-PX (glutathione peroxidase, an enzyme that is part of the antioxidant pathway: if defective, it causes leakage of magnesium and potassium from cells)

- gastro-intestinal dysfunction: there is evidence of objective changes, with delays in gastric emptying and abnormalities of gut motility; there is evidence of swallowing difficulties and nocturnal diarrhoea; there is evidence going back to 1977 of hepatomegaly, with fatty infiltrates: on administration of the copper response test, there is evidence of post-viral liver impairment -- an increase of at least 200 in the copper level is the expected response, but in some severely affected ME/CFS patients the response is zero; there is evidence of infiltration of splenic sinuses by atypical lymphoid cells, with reduction in white pulp, suggesting a chronic inflammatory process; there is evidence that abdominal pain is due to unilateral segmental neuropathy; there is significant evidence that people with ME/CFS have increased serum levels of IgA and IgM against the LPS of gram-negative enterobacteria, indicating the presence of an increased gut permeability resulting in the autoimmunity seen in many ME/CFS patients; this indicates that the symptoms of irritable bowel seen in ME/CFS reflect a disorder of gut permeability rather than psychological stress as most psychiatrists believe (gastro-intestinal problems are a serious concern in ME/CFS, and 70% of the body's immune cells are located in the GI tract)

- reproductive system: there is clinical evidence that some female patients have an autoimmune oophoritis; there is evidence of endometriosis; there is evidence of polycystic ovary syndrome; in men with ME/CFS, prostatitis is not uncommon

- visual dysfunction: there is evidence of latency in accommodation, of reduced range of accommodation and of decreased range of duction (ME patients being down to 60% of the full range of eye mobility); there is evidence of nystagmus; there is evidence of reduced tracking; there is evidence of problems with peripheral vision; there is evidence that the ocular system is very much affected by, and in turn affects, this systemic condition.

The above list is by no means comprehensive but merely gives an overview of documented abnormalities seen in ME/CFS that can be accessed in the literature, all of which is available to the Wessely School.

ME/CFS has been defined in the Canadian Guidelines (2003), which have been adopted internationally and are the best aid to the diagnosis of ME/CFS but which the Chief Investigator Peter White insists should not be used in the UK (see below), perhaps because they are unambiguous:

*'**The question arises whether a formal CBT or GET programme adds anything to what is available in the ordinary medical setting. A well-informed physician empowers the patients by respecting their experiences, counsels the patients in coping strategies, and helps them achieve optimal exercise and activity levels within their limits in a common-sense, non-ideological manner, which is not tied to deadlines or other hidden agenda***".

In its 2007 Clinical Guideline 53 on "CFS/ME", the National Institute for Health and Clinical Excellence (NICE) specifically recommended that the Canadian case definition of ME/CFS should not be used in the UK. NICE based its decision on a small number of mildly positive clinical trials by the Wessely School, while devaluing evidence from scientific studies and patients' own evidence. ME/CFS is the only physical condition for which behavioural modification is the primary (indeed only) management approach in a NICE Guideline. The MRC declines to fund biomedical studies, yet the cost of implementing the Wessely School regime in the UK is £3.75 million annually, in addition to non-recurrent costs of £26.45 million (Breakthrough, MEResearch UK, Spring 2008).

<u>There is no cure for ME/CFS</u>

According to the Chief Medical Officer's Working Group Report on "CFS/ME", there is no cure (CMO's Working Group Report: January 2002: 4.4.2.2:48) so it is misleading of the MRC PACE Trial Principal Investigators to imply otherwise and to try to achieve their aim by using techniques of persuasion in an attempt to control the mind of participants by constantly bombarding them with language that seems to misinform them.

For the Principal Investigators to state that full recovery is possible with CBT/GET, as Professor Michael Sharpe asserted ("*There is evidence that psychiatric treatment can be curative".* BMB 1991:47:4:989-1005) and as Professor Peter White – using "*the General Practice Research Database to show that social factors affect prognosis in CFS"* -- unambiguously asserted ("*recovery from CFS is possible following CBT….Significant improvement following CBT is probable* ***and a full recovery is possible****".* Psychother Psychosom 2007:76(3):171-176), implying that patients <u>can</u> recover from ME/CFS if they would only follow the psychiatrists' recommended regime of CBT/GET, seems to offer false hope: the recovery statistics simply do not support such a belief.

To imply otherwise would seem to be overt misrepresentation of the significant body of peer reviewed published biomedical science.

However, in their 2007 paper Knoop, White et al appear oblivious and confidently state: "*The first clinical implication of the present study is that a therapist delivering CBT can tell the patient that substantial improvement is likely* ***and that full recovery is possible****. By communicating this, the therapist can counterbalance factors that lower the expectations of the patient. Examples of such factors are a negative attitude of certain patient advocacy groups towards behavioural interventions or an oversolicitous* (sic) *attitude of others in response to CFS.* ***There is empirical evidence that lower expectations of patients have a negative influence on therapy outcome****".*

This belief may explain the instructions in the PACE therapists' Manuals for the need for repeated "*positive reinforcement"*.

In the same 2007 paper, White's definition of "recovery" is curious:

"*The second clinical implication of the present study is that recovery is a construction*. ***The percentage of recovered patients differed depending on the definition of recovery used. It is possible that a patient has another concept of recovery than the therapist".***

The Penguin English Dictionary defines "recovery" as "*regaining health after sickness".*

To most rational people, "recovery" means being restored to previous good health, with the ability to return to school, work, sport, social activities and hobbies with no ill-effects. For them, unlike for Peter White, "recovery" is not a negotiable term.

According to US statistics provided in August 2001 by the Centres for Disease Control CFS Programme Update, only 4% of patients had full remission (not recovery) at 24 months.

In 2005, the message was clear: ***"The bitter, unpalatable reality is that ME/CFS patients can be pro-active, they can have a good attitude, they can try various drugs and non-drug interventions, and they can still remain ill, even profoundly disabled"*** (The CFIDS Chronicle Special Issue: The Science & Research of ME/CFS: 2005-2006:59).

In 2007, the ME Association Medical Advisor pointed out that: "*Several research studies looking at prognosis have been published. Results from these studies indicate that ME/CFS often becomes a chronic and very disabling illness, with complete recovery only occurring in a small minority of cases. A recent Systematic Review of 14 studies found a median recovery rate of 7%"* (ME/CFS/PVFS: An exploration of the key clinical issues prepared for health professionals. Drs Charles Shepherd & Abhijit Chaudhuri, published by The ME Association, 2007).

For the Wessely School to offer such people only a management regime that is designed to alter their (correct) perception that they are seriously physically ill, and to imply that restructured thinking and incremental aerobic exercise will result in significant improvement (and even full recovery), is believed by many people to amount to professional misconduct.

ME/CFS causes death

People die from ME/CFS, but not from states of chronic "fatigue" or "CFS/ME" as defined by the Wessely School.

On 13th December 1988 Brynmor John MP died from ME/CFS. His experience of the illness was all too familiar: '*Though there is only a slight gradient from our house to the main road, it could have been the North face of the Eiger. I just could not get up it'.* He found himself unable to dress; the slightest exertion exhausted him and it took days to regain his strength. He was irritated by the profusion of psychiatric comment and was trying to ensure better understanding of ME/CFS (Perspectives, Summer 1991:28-30). Brynmor John suddenly collapsed and died as he was leaving the House of Commons gym after having been advised to exercise back to fitness.

In 1992, Professor Hugh Fudenberg from South Carolina (a pioneer of clinical immunology and one of the most distinguished minds in the field, being awarded The Medal of the Institut Pasteur at the age of 32; he was also a Nobel Prize nominee) stated that there is **"a greater death rate than normals in the same age range"** (The Clinical and Scientific Basis of Myalgic Encephalomyelitis Chronic Fatigue Syndrome: ed. BM Hyde, published by The Nightingale Research Foundation, Ottawa, Canada, 1992: page 644).

This was corroborated 14 years later by Professor Leonard Jason et al, who found that the three most prevalent causes of death in ME/CFS patients were heart failure, suicide and cancer and that the age of death is considerably younger than in the general population (Health Care Women Int 2006:27(2):615-626).

Perhaps the most tragic and well-known death from ME/CFS is that of Alison Hunter from Australia, who died in 1996 and whose death certificate stated the cause of death as "*Severe progressive ME*". She was just 19 years old. The pathologist's report confirmed that she had severe oedema of the heart, liver and brain. She had also suffered severe ulceration to her throat, seizures, paralysis, other neurological symptoms, and gastrointestinal paresis with failure of the gut and bowel. James Ibister, Head of Haematology at Royal North Shore Hospital, Sydney, said: "*To be honest, I felt helpless towards the end. On many occasions I was extremely embarrassed about the way she was treated by the system. A lot of terrible things Alison went through were doctors projecting their own fears and inadequacies. How anyone could not think she had a major medical illness was beyond me*". Alison, he said, suffered "*terrible physical distress compounded by insults and inhumanity"* (www.ahmf.org).

In 1998, an ME/CFS sufferer wrote: "*I've had ME for nearly five years, 18 months of which were a living hell. The physical suffering (inability to walk unaided, chew, swallow, breathe properly, hold my head up, hands which became spastic) was bad enough, but the brain symptoms were at times unbearable – my brain exploding with stimulus until I thought I'd gone mad (and) the room spun like I was drunk, making me feel physically sick. The bed felt like it was moving. I had explosions of light before my eyes. Worst of all were the 'seizures', which felt like I was having a stroke – pins and needles on my head and face, drooping muscles around my mouth, my head would start to tip backwards, absolutely terrifying. I live alone, yet have been refused home care, disability living allowance or any form of medical advice. The public need to be shocked by seeing the severely affected, those being tube fed, shaking, uncontrollable, paralysis, unable to hold up their head, speak, see, control bowel movements.* ***The myth that ME is never fatal must be dismissed. I know of several people who have died of the complications ME can bring****"* (Perspectives, September 1998:26).

UK Coroners are now providing incontrovertible evidence that ME/CFS can lead to death. This is something that the ME/CFS community has known for many years. The UK authorities keep no statistics, so the actual number of deaths from ME/CFS remains unknown.

In 1992, a 30 year old woman in the UK who had suffered from ME/CFS for five years committed suicide; the post-mortem study (using polymerase chain reaction) showed enteroviral sequences in samples from her muscle, heart, the hypothalamus and the brain stem. No enteroviral sequences were detected in any of the control tissues. The researchers stated: "*The findings further support the possibility that hypothalamic dysfunction exists in the pathogenesis of (ME)CFS (and) they suggest that the chronic fatigue syndrome may be mediated by enterovirus infection and that persistent symptoms may reflect persistence in affected organs"* (McGarry et al. Ann Intern Med: 1994:120:11: 972-3).

On 18th June 1995, Consultant Radiologist Dr Eric Booth died from ME/CFS aged 48 years, having had ME/CFS for 16 years. Four years before he died, Booth wrote: "*I have been very seriously ill for the last five years, being totally bedridden (but) am unable to convey this to my medical colleagues. I have come to believe that physicians suffer from compassion fatigue"* (BMJ 28 October 1995:311). The autopsy findings were disturbing but were suppressed; Booth's next of kin was warned by the Official Solicitor that action would be taken against her if she divulged the post-mortem findings, to the extent that she was reduced to a state of chronic fear.

In 1998, there was the well-reported case of Joanna Butler, a young woman aged 24 from Leamington Spa, Warwickshire, who was severely affected by and died from ME/CFS. She was nursed at home by her parents and was bed-bound for the last two years of her life and required tube-feeding. Although she died of ME/CFS, her parents were suspected of having caused her death by administering too high a dose of a medically-prescribed morphine-related compound, and the local paper (Courier) reported that the Warwickshire County Coroner (Michael Coker) ordered a police investigation. This investigation cleared them of blame but they were hounded to such an extent that they were forced to move away from the area (see the press reports in The Observer, 19th March 1998: "Tragic death of young ME victim" and the reports in the local paper, including the Courier, which carried a report on the '*many who die each year'* of ME).

In January 2003 the wife of Richard Senior died of ME/CFS; the North Wales Coroner entered CFS as the cause of death on the death certificate.

On 4th July 2005 Casey Fero died of ME/CFS at the age of 23 in the US. The autopsy showed viral infection of the heart muscle. The pathologist was shocked at the state of Casey's heart, which showed fibrosis indicating the presence of a long-standing infection.

In November 2005 Sophia Mirza died of ME/CFS in the UK and the death certificate of 19th June 2006 gives CFS as the cause of death, with acute renal failure.

Another UK death from ME/CFS occurred in May 2008 when a severely affected and courageous woman died in the North of England; her death certificate gives "**Myalgic encephalomyelitis"** as the cause of death.

Evidence from autopsies of people who have died from ME/CFS is chilling. In Sophia Mirza's case (a 32 year old woman sectioned by psychiatrists who alleged that she was suffering from a mental disorder so she was kept in a locked ward and, according to her mother's evidence, denied basic care), there was evidence of severe inflammation throughout 75% of her spinal cord. This was one of three such autopsies spoken about by Dr Abhijit Chaudhuri at the Royal Society of Medicine meeting on 11th July 2009 (see below).

A 2005 autopsy in the US showed oedema of the lower limbs; the alveolar spaces of the lungs were filled with inflammatory cells and there were small emboli scattered throughout the arteries; there was marked congestion of the liver and spleen; the bowel was ischaemic; there was mild inflammation of the kidneys; there was also evidence of rhabdomyolysis (the breakdown of muscle fibres resulting in the release of muscle fibre contents into the circulation, some of which are toxic to the kidney); the bladder showed a hyperplastic epithelium; the thyroid showed colloid filled follicles, with scattered dystrophic calcifications and calcification of the small arterial walls; the right occipital lobe of the brain showed areas of degeneration and degenerated astrocytes, and the white matter surrounding this defect appeared puckered.

The Medical Director of The National CFIDS Foundation (chronic fatigue immune dysfunction, a commonly-used US term for ME/CFS), Dr Alan Cocchetto, commented: ***"Every time you look closely at someone with this disease, you see immense suffering. There appears to be no limit as to the human toll that this disease is capable of exerting on patients"*** (http://www.ncf-net.org/forum/Autopsy.htm).

The Wessely School, however, including the three PACE Trial Principal Investigators and the Director of the Clinical Trial Unit, continue to believe that ME/CFS is an *"aberrant illness belief"* and they assume that all patients – including those with ME/CFS -- suffering from what they deem to be "medically unexplained symptoms" (which they refer to as MUS) or from "medically unexplained physical symptoms" (which they refer to as MUPS) are really suffering from the same mental illness, ie. somatisation, and as such their symptoms will never be medically explained, therefore there is no point in wasting health service resources in seeking a biomedical explanation.

The Wessely School claim that they are reacting against Cartesian dualism – the long-held belief in Western medicine that an illness is either "organic" or "psychiatric". However, as Dr Mary Schweitzer (a US ME/CFS sufferer and patient advocate) points out, the Wessely School has simply turned Cartesian dualism on its head. Disorders such as schizophrenia used to be regarded as "mental", but advances in understanding now show that the psychiatric disturbances that present in schizophrenia are manifestations of underlying organic pathology. In their own interpretation, the Wessely School has reversed this in relation to ME/CFS, claiming that the physical is psychological which hardly accords with 21st century medicine (http://www.hhs.gov/advcomcfs/meetings/presentations/schweitzer_0509.pdf).

SECTION 1: BACKGROUND TO THE MRC PACE TRIAL

Since 1987, a prominent theme running through the Wessely School's psychiatric literature on "CFS/ME" has been that patients who present with symptoms that the psychiatrists and those they advise (Government agencies and the medical and permanent health insurance industry) wish to eradicate are an "*unjustified*" and "*undeserving*" financial burden, and that it is neither cost-effective, necessary nor appropriate to investigate their "*non-existent*" disorder.

The Wessely School believes that patients with "CFS/ME" have "*dysfunctional thinking*" and "*personality problems*" and are susceptible because of their "*female gender*", and that they must be managed by those who know best (ie. by Wessely School psychiatrists and their adherents) by means of behavioural interventions which include graded aerobic exercise. The basis of the Wessely School's beliefs about "CFS/ME" upon which the PACE trial is based is that, together with fibromyalgia, irritable bowel syndrome, multiple chemical sensitivity and premenstrual syndrome, "CFS/ME" is a one functional somatic syndrome (ie. a behavioural / somatisation disorder) which, due to an *"artefact of medical specialisation"*, naïve clinicians fail to recognise and thus treat as different disorders (S Wessely, C Nimnuan, M Sharpe, Lancet 1999:354:936-939; S Wessely, Psychol Med 1990:20:35-53).

The Wessely School assumes that a person's thoughts are dictating their feelings, so the objective is to modify the patients' thoughts in order to effect a cure. However, the concept that "thinking" changes "behaviour" has never been proven.

To quote William M Epstein, Professor in the School of Social Work at the University of Nevada: ***"the central notion of causal direction, that cognition rules emotion, behaviour, and perhaps even physiology, has not been adequately proven by any test"***.

According to Epstein, CBT is: *"barren of credible evidence to support its efficacy"* and *"the best research offers no credible evidence of any successful psychotherapy for any condition"*. He says: *"CBT is constantly pressing, chiding, encouraging, and inveighing the patient, through the demands of the therapeutic relationship, to believe, believe, believe in the curative ability of treatment and the authority of the therapist"* and he says: "*This is precisely the promise of organisations seeking members: your current behaviour is wrong (and) we can teach you better ways of living"*.

Epstein points out that advocates of CBT are *"choosing the benefits of subjectivity over the trials of objective proof"* (Psychotherapy as Religion (Chapter 9), University of Nevada Press, Reno, Nevada, 2006).

The Wessely School and the MRC, however, seem oblivious of the work of Epstein. Their proselytizing has gone on for over two decades yet has failed to produce any evidence to support their theories about ME or any cure for patients, perhaps because their use their own definition which excludes people with signs of neurological disorder, as occur in ME.

The Wessely School Perspective

The MRC PACE Trial is managed by a Trial Management Group, most of whose members are considered to support the beliefs of the Wessely School and, as noted above, Wessely himself will oversee the PACE Clinical Trial Unit.

Wessely himself set up and directed The Mental Health & Neuroscience Clinical Trials Unit in 2002. It is the first in the UK to specialise in mental health and the neurosciences. In its first six years of operation it has provided advice and support to a large number of grant applications, which may explain why, despite the MRC's denial of bias, approximately 91% of its total grant spend on "CFS/ME" since 2002 (over £3 million) was awarded to psychiatric trials of behavioural interventions and why at least 33 funding applications for

biomedical aspects of ME/CFS were rejected, many of which were submitted by established researchers with a sound track record (Breakthrough, MERUK, Autumn 2008:8).

It is a matter of record that Wessely – together with members of the Wessely School – firmly believes that ME does not exist, and it is his intention to ensure that it is eradicated as a nosological entity.

On 15th April 1992 Wessely spoke at a Pfizer/Invicta symposium held at Belfast Castle (Eradicating "Myalgic Encephalomyelitis"), where he said that ME sufferers prefer to feel that they have a 'real' physical disease – it is better for their self-esteem, and that the label ME helps legitimise patients' dealings with doctors. Referring to a programme of graded exercise for ME patients, he said there were *"a very large number of drop-outs from treatment,* ***largely related to the fear these patients had, albeit inappropriately, of accepting that their disorder was 'all in the mind'*** *".* Nothing could be clearer: the conference report records that Wessely stated that ME patients' fear of accepting that their disorder was 'all in the mind' was 'inappropriate'.

In 1993 Wessely wrote in The Lancet: *"The inclusion (in ICD-10) of benign myalgic encephalomyelitis as a synonym for postviral fatigue under Diseases of the Nervous System seems to represent an important moral victory for self-help groups in the UK…Neurasthenia remains in the Mental and Behavioural Disorders chapter under Other Neurotic Disorders…Neurasthenia would readily suffice for ME"* (Lancet 1993:342:1247-1248).

In April 1994 when Wessely delivered the 9th Eliot Slater Memorial Lecture at the Institute of Psychiatry ("Microbes, Mental Illness, the Media and ME: the Construction of Disease"), he claimed dual classification in the ICD: "*in a masterstroke of diplomacy it will be listed in the new revision of ICD-10 twice, once under neurology, and once under psychiatry"*, an assertion which the WHO confirmed was incorrect.

In his lecture, Wessely made his position clear: ***"I will argue that ME is simply a belief, the belief that one has an illness called ME….. .I will argue that this line here*** (overhead slide) ***represents not the line between low and high cortisol responses (but) the line between real and unreal illness".***

Having linked ME to neurasthenia earlier in his lecture, Wessely then said: "*there is another condition with which ME might easily be confused, and it is hysteria"*. Referring to the Royal Free outbreak of ME in 1955, he continued *"Royal Free disease is itself part of the world of myth…..It is a tragedy that the label of ME has been transferred from (the Royal Free outbreak to CFS), and brought with it its burden of hysteria…..Organic diseases lose their credibility as their psychological causes are recognised"*. He also said: "*No matter how bad doctors are, sufferers still need to keep going – doctors are still the main passport to acceptance and validation of suffering, not least because we control access to support and benefits"* (http://www.meactionuk.org.uk/wessely_speech_120594.htm).

In 1995, Wessely stated: "*As an observer of the social scene, I know that ME is defined by the sufferers themselves*" and he described ME as *"a social belief system"* (JCFS 1995:3:2:111-122).

However, on 6th August 2002 the WHO confirmed that ME will stay in the neurological section as a disorder of the brain and that the WHO has no plans to reclassify it as a psychiatric disorder in any forthcoming revision of the ICD.

Despite the Wessely School's refusal to accept the WHO classification (which is mandatory in the UK) and their incorrect advice to Government Ministers, as a result of clarification by the WHO, Ministers were forced to correct their own misinformation and on 11th February 2004 the Health Minister, then Lord Norman Warner, formally confirmed that the correct classification for the disorder (referred to by the Minister as "CFS/ME") remains neurological.

The ME Association Newsletter of March 2004 stated: *"The issue mattered because the psychiatrists had stifled access to research funds for any UK researchers wanting to study organic causes*".

Apparently unheeding, in 2006 Wessely stated: ***"Like it or not, (ME) CFS is not simply an illness, but a cultural phenomenon and metaphor of our times"*** (Psychol Med 2006: 36: (7):895-900).

Commenting on this, ME/CFS advocate Peter Kemp from the UK noted: "*It is not (ME) CFS that is a metaphor of our times. It is the researchers' attitude that is a metaphor of ALL times"* and he considered how the Wessely School think about patients with (ME)CFS: "*Here is a group behaving in a way that I don't like. Shall I find out what is wrong by listening and learning? No. I'll make a judgment and then prove that I am right. It is this exact attitude that led to the rise of fascism and has been the cause of victimisation of the weak and minorities in known history….The frequent discrimination and abuse experienced by people with ME/CFS at the hands of the medical profession, researchers, benefits agencies, the media and society at large make a diagnosis of ME/CFS a social curse"* (Co-Cure ACT: 16th June 2006).

Seemingly unmoved by the ever-mounting body of evidence that he is wrong, in 2007 (ie. during the life of the MRC PACE Trial), Wessely co-authored a chapter on Functional Somatic Syndromes with Lisa Page in which he included chronic fatigue syndrome (chapter 7: pp 125-136 in "Handbook of Liaison Psychiatry" edited by Geoffrey Lloyd and Elspeth Guthrie, CUP 2007).

It is notable that although the disorder is referred to as "chronic fatigue syndrome", Page and Wessely are clearly referring to and including ME and indeed, ME/CFS self-help support groups are mentioned in their references.

Chapter 7 includes the following extracts:

"*Functional somatic syndromes: definition and terminology*

"The functional somatic syndromes refer to a number of related syndromes that have been characterised by the reporting of somatic symptoms and resultant disability rather than on the evidence of underlying conventional disease pathology….all however share the feature of a disconnection between subjective symptomatology and objective biomedical pathology.

"Chronic fatigue syndrome, irritable bowel syndrome and fibromyalgia have been more extensively researched than most other FSS which has led to specific pathophysiological mechanisms being advanced for each. Nevertheless…it remains the case that the similarities between the different FSS are sufficiently striking for there to be a compelling case for considering them together (Barksy & Borus, 1999; Wessely et al, 1999).

"The standard (medical) diagnostic criteria for FSS usually require specific symptoms to be present, whereas psychiatric classification (under the somatoform disorders) emphasises the number of symptoms.

"Patients with FSS have been rated as one of the three most common types of patients that are 'difficult to help' (Sharpe 1994)….The tendency of those with FSS to turn to alternative medicines for treatment is likely to be …because alternative remedies often endorse the FSS patient's own physical illness attributions (Moss-Morris et al 2003).

"*Illness beliefs*

"At present, chronic fatigue syndrome is the functional somatic syndrome for which there is most evidence that beliefs about the illness may impact on the course of the illness itself. Patients with chronic fatigue syndrome are more likely to make physical illness attributions (rather than normalising or psychologising attributions) for a selection of common symptoms compared to controls (Butler et al 2001) and are more likely to believe their illness will be chronic…

"These beliefs and attitudes about symptoms may act as a mechanism that then guides the patient to adopt avoidant behaviours….In fact, it is a change to beliefs about avoidance…that predicts good outcome from cognitive behavioural therapy in chronic fatigue syndrome (Deale et al 1998), highlighting the need for more research into the way illness attributions maintain ill-health.

"Social factors

"Several of the functional somatic syndromes, including chronic fatigue syndrome, GWS (Gulf War Syndrome) and repetitive strain injury have gained public credibility in spite of widespread medical scepticism as to their very existence. This phenomenon has been attributed to changes within society, including the erosion of the physician's traditional role…Patient support groups…may have some negative consequences, for example, membership of a chronic fatigue syndrome support group has been associated with poorer prognosis (Bentall et al 2002, Sharpe et al 1992).

The financial 'reward' to be gained from disability payments or litigation has been argued as playing a role in the maintenance of ill health in those suffering from functional somatic syndromes…For example being in receipt of sickness benefit has been shown to be a poor prognostic sign in chronic fatigue syndrome (Bentall et al 2002, Cope et al 1994).

"Treatments

"Psychosocial treatments such as cognitive behavioural therapy have been shown to be beneficial in a range of somatoform disorders…including the most researched functional somatic syndromes (i.e. chronic fatigue syndrome, irritable bowel syndrome and fibromyalgia).

"Conclusion

"The functional somatic syndromes share many similarities in terms of symptomatic overlap and effective treatments as well as non-symptomatic characteristics; these observations imply that it may be unhelpful to regard each as a separate condition".

The book won the 2008 British Medical Association prize in Mental Health and, as customary with books ascribing ME/CFS to a somatoform disorder, it received glowing reviews, for example:

- *"All budding and established liaison psychiatrists should have this manual and medical libraries should stock it"* (British Medical Journal)

- *"It will be essential reading for liaison psychiatrists, liaison nurses, other members of the mental health team and services managers"* (Clinical Medicine Journal of the Royal College of Physicians of London)

- *"This book is a very welcome addition to liaison psychiatry literature. It is the first really comprehensive textbook of liaison psychiatry by authors predominantly working in the UK….Were I to recommend a single liaison psychiatry textbook, it would be this one"* (The British Journal of Psychiatry).

Given that the book contains so much misinformation about ME/CFS, these reviews are troubling.

Apparently unheeding of the WHO, Wessely remains adamant that "CFS/ME" is the same disorder as neurasthenia.

As recently as 2009 he wrote: "*I run a clinic for sufferers with chronic fatigue syndrome (CFS), sometimes also called myalgic encephalomyelitis (ME),* ***and known to a previous generation of neurologists as neurasthenia***" (Wessely S [2009]. Surgery for the treatment of mental illness: the need to test untested theories. http://www.jameslindlibrary.org/trial_records/20th_Century/1920s/kopeloff/kopeloff-commentary.html).

The Wessely School often assert that it is only patients who disagree with their hypothesis (which instantly confers disparagement upon patients), but they do not refer to the countless mainstream psychiatrists, psychologists, neuroscientists, immunologists and other biomedical scientists who certainly disagree with their hypothesis (see Co-Cure RES: 14th September 2009, and see also Section 2 below).

Common threads running through the Wessely School's documents are their refusal to heed publicly-expressed concern about what is described as their flawed methodology, and their ignoring of the copious published evidence that disproves their insistence that ME/CFS is a behavioural disorder.

In a recent article, Wessely states: *"there is also a second and more disturbing explanation for the alacrity and uncritical nature with which* (organic) *explanations are endorsed on often the flimsiest of evidence. Psychiatry, its patients and its practitioners, continue to be stigmatised like no other branch of medicine...**If one reads the angry responses to any article that mentions chronic fatigue syndrome and psychiatry in the same breath, it is clear that the drive to find an* **(organic)** *biomarker for chronic fatigue syndrome is driven not so much by a dispassionate thirst for knowledge but more by an overwhelming desire to get rid of the psychiatrists**… indeed, the search for infective causes and triggers for psychiatric disorders has never ceased."* (http://www.jameslindlibrary.org/trial_records/20th_Century/1920s/kopeloff/kopeloff-commentary.html).

Inevitably, the desperation of people with ME/CFS to show how erroneous is the Wessely' School's psychosocial model of "CFS/ME" is escalating.

Wessely seems to take patients' "*drive to find a biomarker*" quite personally (a "drive" which is shared by internationally respected doctors and scientists) and appears unable to perceive any explanation other than ME/CFS patients' "*overwhelming desire to get rid of the psychiatrists*".

Wessely appears to be so blinded by the supposed benefits afforded by a diagnosis of ME/CFS that he overlooks the simple fact that the patient's life - in every respect - is devastated by the illness. The suffering and disruption are such that many patients could not care less about what the solution might be as long as they can improve or recover. To imply that patients would reject help because it happened to come from a psychiatrist is ludicrous.

Patients with ME/CFS are not opposed to psychiatry or psychiatrists. Patients are opposed to the 'Wessely School' because the theories they have espoused for over two decades do not help them and do not accord with the biomedical science that underpins ME/CFS.

It seems that no matter how much evidence is presented, and no matter how many times the WHO repudiates their misinformation, Wessely and other members of the Wessely School refuse to accept it and they continue to insist that ME, which they include as part of "CFS/ME", is a mental illness.

It is the Wessely School ethos that underpins the MRC PACE Trial.

As Dr Monica Greco, Senior Lecturer in the Department of Sociology, Goldsmith's College, University of London, suggests: "*..are there ways in which the privilege accorded to aetiology may actually hinder the delivery of better care in many situations?…..the immediate focus on…treatments often constitutes a 'knee-jerk' reaction dictated by factors that have little to do with the best interest of the patient.* ***Indeed, physical evidence – or lack thereof, as supposedly 'proved' by negative test results – is often used to better dismiss patients and their concerns rather than vice-versa****"* (Co-Cure ACT 12th September 2009).

That this occurs in ME/CFS is beyond dispute, so the question requiring an answer is <u>why</u> is it occurring?

It is a matter of record that Wessely School psychiatrists have close links to powerful medical and permanent health insurance companies such as UNUMProvident, which has been described as an "*outlaw company*" by California Insurance Commissioner John Garamendi – see below. If it can be "proven" that "CFS/ME" is a mental disorder, then insurance payments to patients could be limited or even denied. Given the rise in the number of claims for ME/CFS, this is a not insignificant matter from the insurers' perspective.

Despite the substantial evidence-base that ME/CFS is a multi-system organic disorder, the Wessely School continue to insist that, along with big ears, freckles and boredom, ME is a "*non-disease*" that is best left untreated (BMJ 2002:324:883-885).

Thus when the Wessely School and the agencies they advise, including the MRC and the National Institute for Health and Clinical Excellence (NICE), refer to "CFS/ME", they are in reality referring to "chronic fatigue", not to the specific disorder ME/CFS, yet the Wessely School insist that they are including patients with ME in their studies, and they assert: *"CFS has officially replaced the term M.E"* (http://www.kcl.ac.uk/projects/cfs/patients/), an assertion that as far as the WHO is concerned is patently untrue.

In 1991, the Wessely School produced their own case definition of "CFS" (JRSM 1991:84:118-121) that fails to distinguish between ICD-10 G93.3 and ICD-10 F48.0: it expressly excludes those with neurological disorders but expressly includes those with "chronic fatigue" as seen in numerous psychiatric disorders.

Because they have broadened the case definition to include anyone with "chronic fatigue", many believe it unacceptable that Wessely School psychiatrists continue to exert a monopoly on ME/CFS research in the UK when the international evidence does not support their hypothesis about the nature of it.

The Wessely School's views on "CFS/ME" are summarised by psychiatrist Dr Anthony Cleare, Head of Neurobiology of Mood Disorders Section at the Institute of Psychiatry (IoP):

"Efforts to define valid subgroups have not yet been fruitful. Differences do exist between the minority of cases with long illness histories, severe disability and multiple symptoms, who show overlap with the concept of somatisation disorder, and the larger group with less disability, fewer symptoms and shorter illness durations, who have a better prognosis" (http://www.iop.kcl.ac.uk/iop/prt/cfs.htm).

At least 25% of sufferers (hardly a "*minority*") are severely and chronically affected, but Cleare reveals the Wessely School's belief that the more sick and disabled a person with ME/CFS, the more s/he is deemed to have a somatisation (ie. a behavioural) disorder.

Illustrations of Wessely's Words

For the avoidance of doubt, some illustrations of Wessely's published views about ME/CFS patients include the following:

"Though disordered immunity and persisting viral infection have recently attracted attention, it is important that immunologists do not deflect attention away from the wider (ie. psychiatric) aspects of the chronic fatigue / postviral syndrome" (Anthony David, Simon Wessely, Anthony Pelosi. Lancet 1988:July 9th: 100-101).

"*My local book shop has just given ME the final seal of approval, its own shelf. A little more psychology and a little less T cells would be welcome"* (Wessely S. BMJ 1989:298:1532-1533).

"Many patients referred to a specialised hospital with chronic fatigue syndrome have embarked on a struggle. One of the principal functions of therapy at this stage is to allow the patient to call a halt without loss of face… The patient should be told it is now time to 'pick up the pieces' (and) the process is a transfer of responsibility from the doctor to the patient, confirming his or her duty to participate in the process of rehabilitation in collaboration with the doctor" (Simon Wessely, Anthony David, Trudie Chalder et al. JRCP 1989:39:26-29).

"*…external attribution protects the patient from being exposed to the stigma of being labelled psychiatrically disordered, (affording) diminished responsibility for one's own health…Inappropriate referrals to physicians can lead to*

extensive physical investigation that may then perpetuate the… pattern of physical attribution" (R Powell, R Dolan, S Wessely. J Psychsom Res 1990:34:6:665-667).

"It is this author's belief that the interactions of the attributional, behavioural and affective factors is responsible for both the initial presentation to a physician and the poor prognosis" (Chronic fatigue and myalgia syndromes. Wessely S. In: Psychological Disorders in General Medical Settings. Ed: N Sartorius et al. Hogrefe & Huber, 1990).

"Suggestible patients with a tendency to somatize will continue to be found among sufferers from diseases with ill-defined symptomatology until doctors learn to deal with them more effectively" (Simon Wessely. Psychological Medicine 1990:20:35-53).

"The description given by a leading gastroenterologist at the Mayo Clinic remains accurate: ***'The average doctor will see they are neurotic and he will often be disgusted with them'*** *"* (Wessely S. In: Psychological Disorders in General Medical Settings. Ed: N Sartorius et al. Hogrefe & Huber, 1990).

"Continuing attribution of all symptoms to a persistent 'virus' preserves self-esteem" (Butler S, Chalder T, Wessely S et al. JNNP 1991:54:153-158).

"*The prognosis may depend on maladaptive coping strategies and the attitude of the medical profession"* (Wessely S. Pulse of Medicine 14th December 1991:58).

*"Blaming symptoms on a viral infection conveys certain advantages, irrespective of its validity….It is also beneficial to self-esteem by protecting the individual from guilt and blame. The germ has its own volition and cannot be controlled by the host. The victim of a germ infection is therefore blameless…Many patients become hypervigilant and over-sensitised to physical sensations….The behaviour of family and friends may inadvertently reinforce the sick role… Fear of illness is an important part of (the disorder)…****the approach we favour is provided by professionals whose training and background is mental health****"* (Simon Wessely, Trudie Chalder et al. In: Post-viral Fatigue Syndrome. Ed: Rachel Jenkins and James Mowbray. John Wiley & Sons, Chichester, 1991).

"Validation is needed from the doctor. Once that is granted, the patient may assume the privileges of the sick role – sympathy, time off work, benefits etc" (Wessely S. Reviews in Medical Microbiology 1992:3:211-216).

"Studies usually find a high prevalence of psychiatric disorder among those with CFS, confirming that physicians are poor at detecting such disorders" (Lewis G, Wessely S. Journal of Epidemiology and Community Health 1992:46:92-97).

*"Most doctors in hospital practice will be familiar with patients who complain about a wide variety of symptoms but whose physical examination and investigations show no abnormality. (Such) symptoms have no anatomical or physiological basis….****Patients with inexplicable physical symptoms are…generally viewed as an unavoidable, untreatable and unattractive burden****"* (Alcuin Wilkie, Simon Wessely. Brit J Hosp Med 1994:51:8:421-427).

"***Wessely sees viral attribution as somatisation par excellence"*** (Helen Cope, Anthony David, Anthony Mann. Journal of Psychosomatic Research 1994:38:2:89-98).

"The epidemiology of environmental illness is reminiscent of the difficulties encountered in distinguishing between the epidemiology of myalgic encephalomyelitis (ME), a belief, *and chronic fatigue syndrome, an operationally-defined syndrome* (note that the World Health Organisation does not regard ME as "*a belief"* but as a neurological disorder)…*These patient populations recruited from the environmental subculture are a subgroup of patients who can be expected to show unusually strong beliefs about the nature of their symptoms, associated with a high percentage of psychiatric disorder…****These total allergy syndromes are akin to culture-bound syndromes afflicting modern developed societies where sufferers from unexplained symptoms no longer see themselves***

as possessed by devils or spirits but instead by gases, toxins and viruses" (LM Howard, S Wessely. Clinical and Experimental Allergy 1995:25:503-514).

*"Chronic fatigue may be better understood by focusing on perpetuating factors and the way in which they interact in self-perpetuating vicious circles of fatigue, behaviour, beliefs and disability…**The perpetuating factors include inactivity, illness beliefs and fear about symptoms (and) symptom focusing…CFS is dogged by unhelpful and inaccurate illness beliefs, reinforced by much ill-informed media coverage; they include fears and beliefs that CFS is caused by a persistent virus infection or immune disorder***" (Anthony J. Cleare, Simon C. Wessely. Update 1996:14th August: 61).

"*The term ME may mislead patients into believing they have a serious and specific pathological process…Several studies suggest that poor outcome is associated with social, psychological and cultural factors…We have concerns about the dangers of labelling someone with an ill-defined condition which may be associated with unhelpful illness beliefs…**No investigation should be performed to confirm the diagnosis***". (Simon Wessely, Peter White, Leszek Borysiewicz [now Chief Executive of the MRC], Anthony David, Tim Peto et al. Report of a Joint Working Group of the Royal College of Physicians, Psychiatrists and General Practitioners. RSM (CR54), 1996.

*"The clinical problem we address is the assessment and management of the patient with a belief that he/she has an illness such as CFS, CFIDS or ME…**The majority of patients seen in specialist clinics typically believe that their symptoms are the result of an organic disease process…Many doctors believe the converse**…(Patients') beliefs are probable illness-maintaining factors and targets for therapeutic intervention…many patients receive financial benefits and payments which may be contingent upon their remaining unwell…An important task of treatment is to return responsibility to the patient for management and rehabilitation without inducing a sense of guilt, blame or culpability for his / her predicament"* (Sharpe M, Chalder T, Wessely S et al. General Hospital Psychiatry 1997:19:3:185-199).

"In a previous era, spirits and demons oppressed us. Although they have been replaced by our contemporary concern about invisible viruses, chemicals and toxins, the mechanisms of contagious fear remain the same…To the majority of observers, including most professionals, these symptoms are indeed all in the mind" (Editorial: Simon Wessely. NEJM 2000:342:2:129-130).

*"The greater the number of symptoms and the greater **the perceived disability**, the more likely clinicians are to identify psychological, behavioural or social contributors to illness…**If the chronic fatigue syndrome did not exist, our current medical and social care systems might force us to invent it***" (Wessely S. Annals of Internal Medicine 2001:134:9S:838-843).

"***It is only human for doctors to view the public as foolish, uncomprehending, hysterical or malingering****….One challenge arises when patients have named their condition in a way that leaves doctors uncomfortable, as occurred with chronic fatigue syndrome**….It may seem that adopting the lay label (ME) reinforced the perceived disability. A compromise strategy is 'constructive labelling'; it would mean treating chronic fatigue syndrome as a legitimate illness while gradually expanding understanding of the condition to incorporate the psychological and social dimensions**. The recent adoption by the UK Medical Research Council and the chief medical officer's report of the term CFS/ME reflects such a compromise, albeit an uneasy one"* (B Fischhoff, S Wessely. BMJ 2003:326:595-597).

"*This paper proposes that well-intentioned actions by medical practitioners can exacerbate or maintain medically unexplained symptoms (MUS). This term is now used in preference to 'somatisation'**…. The adoption of a label such as CFS affords the sufferer legitimacy – in other words, it allows entry into the 'sick role'**…. If sections of the media advocate an exclusively organic model, as has happened with CFS, the biomedical model may become firmly enshrined for patients and families at the expense of the psychosocial model***" (LA Page, S Wessely. JRSM 2003:96:223-227).

"***Functional somatic syndromes….include chronic fatigue syndrome****….Perpetuating factors have particular importance in understanding CFS…Physical deconditioning as a consequence of reduced activity may contribute towards greater experience of symptoms"* (Hyong Jin Cho, Simon Wessely, Rev Bras Psiquiatr 2005:27:3).

These are barely illustrative of Professor Wessely's recorded beliefs about ME/CFS, with which the literature is replete.

It is perhaps worth putting on record that following publication of some quotations from Wessely's own articles in CFIDS Chronicle (Spring 1994:14-18 – see below), Simon Wessely wrote: "*If you must quote, do it accurately. I was v(ery) upset by CFIDS --- currently meeting Counsel for the MDU* (Medical Defence Union). *I don't mind what people write about me providing they are accurate with the facts"* (personal communication). Given that it was Wessely's own work that was quoted, his comment was remarkable.

It is also understood that in 1989, Wessely sought an injunction to compel the publishers of Dr Anne Macintyre's book "ME-PVFS: how to live with it" (Unwin Paperbacks) to remove the section that documented his own involvement with the case of Ean Proctor (see below) and republish without reference to himself, with which they duly complied, although copies of the first edition remain in existence.

It is the case that Wessely threatened the charity Westcare (now subsumed within Action for ME) who were at that time the UK distributors of CFIDS Chronicle with an injunction unless they defaced every copy and removed an article entitled "The Views of Dr Simon Wessely on ME: Scientific Misconduct in the Selection and Presentation of Available Evidence?" (Spring 1994:14-18) before sending out the Chronicle, which Westcare duly did. This was confirmed by Richard Sykes himself (for Sykes' further involvement in ME issues, see below), who said that his charity could not run the risk of legal proceedings by Wessely and who then wrote to CFIDS Chronicle in support of Wessely and asked that the Chronicle publish an apology to Dr Wessely in the next issue (a request that was declined by the Editors of the Chronicle). People in the UK complained that copies for which they had paid in advance had been defaced without an injunction requiring such action. However, copies of the CFIDS Chronicle that were mailed directly from the US were not similarly defaced and in fact, the furore drew even more attention to the article.

In October 2009 the premier journal Science published evidence that a gamma-retrovirus XMRV (related to the HIV/AIDS virus – see below) has been found in patients with ME/CFS, a profoundly important discovery about which Simon Wessely was instantly publicly dismissive (see below).

Following the discovery of XMRV by the Whittemore Peterson Institute for Neuro-Immune Diseases, the Institute issued a statement: "*Does (XMRV) prove once and for all that ME/CFS is not a psychological or psychosomatic illness as described by those who don't understand the disease? Absolutely! Actually there are thousands of research articles showing the very real biological problems that ME/CFS patients experience.* ***Only the most stubborn and misinformed individuals refuse to believe that this disease is real and serious****"* (http://wpinstitute.org/xmrv/xmrv_qa.html).

Notably, Dr Jacob Teitelbaum from the US commented: "*The XMRV research helps make it even clearer how real and devastating (ME)CFS is.* ***This may offer a bit more to silence the nitwits who like to claim (ME)CFS is all in your mind (though I would not count on it, as they have ignored reams of earlier research showing (ME)CFS/FMS to be very real illnesses)****"* (Co-Cure Res: 30th October 2009).

For over two decades, the Wessely School have ascribed the symptoms of "CFS/ME" to somatisation.

Lipowski defined somatisation as: *"a tendency to experience and communicate somatic distress and symptoms unaccounted for by pathological findings, to attribute them to physical illness, and to seek medical help for them"* (Am J Psychiat 1988:145:1358-1368). His concept is widely accepted, especially in psychiatry (a discipline that is more of an art than a science).

However, as Crombez G et al point out: ***"it is at worst presumptuous and potentially dangerous to infer the presence of other key features of somatisation from the mere presence of physical symptoms"*** (PAIN: Epub ahead of print, 7th May 2009). They continue: "*Poorly constructed science that….over-simplifies complex constructs does not advance a field of enquiry…**the failure or absence of a biological account of pain is an insufficient reason to promote a psychological account"***. Crombez et al conclude, as so many others have previously concluded, that: "***The current operational use may unduly lead to a 'psychologisation' of physical complaints**".*

Also of interest is the observation of Goodheart and Lansing (Treating People With Chronic Disease: A Psychological Guide. American Psychological Association 1996: pp.98-99): *"Therapists may not use total denial very often, but many deny either a partial reality or the severity of illness. The denial serves as a defense against helplessness**. Therapists are quite capable of constructing a wall of denial, which is evident when they ignore information about the disease and assume a psychosomatic origin, which they believe they can cure**."*

In relation to ME/CFS, such observations seem to be disregarded by the Wessely School. Instead, their continued over-reliance on the concept of somatisation is nurtured by their insistence that there should be no investigations performed on ME/CFS patients other than very basic screening. Since no abnormalities are likely to emerge on routine screening tests, a challenge to their theory cannot be effectively mounted on the basis of abnormal test results in a clinical setting, so patients continue to suffer inappropriate dismissal of their symptoms.

On the basis that what is not looked for will not be found, in her response to the 1998 Joint Royal Colleges' Report on Organophosphates (CR67) with which members of the Wessely School were involved, the Countess of Mar asked: *"Why should the doctor and patient accept the limitations of scientific knowledge? Who is to say that their searches are likely to be futile? I simply ask whether we would have been able to cure TB, eradicate smallpox, prevent the infectious diseases of childhood or establish the link between asbestos and lung disease if the medical practitioners of the time had accepted the limitations of scientific knowledge. After all the evidence the working party heard and read, where is its natural curiosity? It repeatedly mentions that there is a lack of causality, yet it makes no recommendations for causal research. Is this because…it does not wish to know?"* (Hansard [Lords]: 9th December 1998:1011-1024).

It is notable that the Joint Royal Colleges' Report on OPs made almost identical recommendations to those made two years earlier in the Joint Royal Colleges' Report (CR54) on "CFS": regarding diagnosis, physicians were warned against "*over-investigation"* which "*may bias the consultation towards a narrow physical orientation"*; regarding management, physicians were warned against *"multiple referrals from specialist to specialist"* and that *"the management plan does not need to presuppose a particular aetiology"*; regarding treatment, physicians were advised to use *"cognitive behavioural techniques to counteract beliefs and subsequent behaviours which may develop (and which may) serve to perpetuate (symptoms)"*, with physicians being warned that treatment entails *"identifying and modifying illness beliefs, fears and anxieties that may prolong disability"*. Inevitably, symptom continuation was blamed on the patient's attributions, and future research was to be on behavioural interventions. No mention was made of the known neurotoxicity of OPs.

It is of significance that organophosphates have since been shown to cause reproducible alterations in gene regulation, especially in those genes associated with immune, neuronal and mitochondrial function (N Kausnik, ST Holgate and JR Kerr et al. J Clin Pathol 2005:58:826-832).

The organophosphate issue is not the only major health issue about which the Wessely School have been comprehensively shown to be wrong; other examples are Gulf War Syndrome and the Camelford drinking water issue.

Simon Wessely is on record more than once as denying the existence of Gulf War Syndrome (GWS, known in the US as Gulf War Illness). In their official report (Lancet 1999:353:169-178), Unwin, Hotopf, David and Wessely et al, despite having performed no clinical examination or laboratory investigations on the veterans,

concluded that there is no such thing as Gulf War Syndrome, and that one pathway of subsequent illness could be the *"perceived"* risk of chemical attack and that this *"psychological"* effect might be contributing to the increased level of ill-health in Gulf War veterans. This was disproved by a 1999 study carried out for the US Defense Department by Dr Beatrice Golomb for the Rand Corporation which found that pyridostigmine bromide tablets (NAPPS) that the troops were forced to take could not be ruled out as causative (see Denigration by Design? Volume II (Up-date), November 1999: http://tinyurl.com/byn3fn).

UK soldiers were given ten vaccines plus five or six undeclared (and unknown) injections (all records of which have been destroyed or kept by the Ministry of Defence); US soldiers had seventeen vaccines by injection. No informed consent was given by the soldiers. All the toxic substances to which Gulf War veterans were exposed affect the central nervous system and – with the exception of depleted uranium – they also affect the peripheral nervous system; some affect the autonomic nervous system, the cardiovascular system and the blood. By 1999, 9,000 previously fit and healthy Gulf War veterans had died, by which time there were 230,000 medical cases.

In 2008 Wessely et al were conclusively shown to be wrong about Gulf War Syndrome: a report commissioned by the US Congress from The Research Advisory Committee on Gulf War Veterans' Illnesses, chaired by JH Binns and authored by Beatrice Golomb, Daniel Clauw et al (Gulf War Illness and the Health of Gulf War Veterans: Scientific Findings and Recommendations; Washington DC; US Government Printing Office, www.va.gov/RAC-GWVI) concluded **that Gulf War Illness is causally related to exposure to organophosphates and pyridostigmine bromide (PB / NAPPS tablets).** This is a proven example of misattribution by Wessely et al.

Wessely has been shown to be equally wrong about the Camelford drinking water incident, which he dismissed as mass hysteria. In July 1988 twenty tonnes of aluminium sulphate were pumped into the drinking water supplies of the Cornish town of Camelford. Ninety minutes later, a 140-square mile area was affected by Britain's worst water pollution. Residents and visitors immediately suffered distressing symptoms including nausea and vomiting, diarrhoea, stinging eyes, mouth ulcers that took weeks to heal, skin rashes, peeling skin and lips sticking together, followed by musculoskeletal pains, malaise and impairment of memory and concentration. In some cases, hair, skin and nails turned blue; bone showed stainable aluminium over six months later.

In the Camelford incident, initially seven people died, 25,000 people suffered serious health effects and 40,000 animals were affected (The Ecologist 1999:20:6:228-233). It is since thought that at least 20 people died from drinking the contaminated water (Sue Reid, Daily Mail, 14th December 2007).

An article by Bernard Dixon in the British Medical Journal (BMJ 1995:311:395), based on a "re-assessment" of the Camelford incident by psychiatrists Anthony David and Simon Wessely (Psychosomatic Research 1995:39:1-9) stated: *"mass hysteria was largely responsible for the furore"* and claimed that David and Wessely's article *"helps to sort out facts from fiction"*. David and Wessely's article found that anxiety was the cause of the symptoms and that there was no evidence of long-term adverse effects on health as a consequence of the water contamination. Typically,*"sensational reporting"* by the media was held to be a significant factor.

Although noting that some peoples' hair, skin and nails turned blue, in their paper Wessely and his co-author Anthony David claimed that the "somatic" symptoms were the result of heightened perception of normal and benign symptoms and irresponsible reporting by the press, though they did not explain by what mechanism hysteria affects animals.

In 1999 it was conclusively shown by Paul Altmann et al that there was objective evidence of considerable organic brain damage compatible with the known effects of exposure to aluminium and that it was this exposure, not anxiety or hysteria, which was the cause of the symptoms exhibited by those who had been exposed to the contaminated water (BMJ 1999:319:807-811).

Professor Anthony David's response to this was notable; he stated that Altmann et al's result overlooked *"the bias inherent in self-selection of cases"* and "*the cases may already have had unexplained symptoms and cognitive problems"*. Anthony David (Professor of Cognitive Neuropsychiatry at Guy's King's and Thomas' School of Medicine, where he works with Wessely) also said: "*The reopening of the Camelford case is regrettable as the people concerned may worry anew about their health"* (BMJ 2000:320:1337).

The death toll has since risen – see The Daily Telegraph, 20th April 2006: "*Alzheimer's fear grips poisoned water town*" by Medical Editor Celia Hall.

More recently, Exley and Esiri described severe cerebral congophilic angiopathy coincident with increased brain aluminium in a resident of Camelford (JNNP 2006: doi:10.1136/jnnp.2005.086553), causing Walter Lukiw, Associate Professor of Neuroscience at Louisiana State University Health Sciences Centre, to note that as over-expression of stress-sensing, pro-inflammatory and pro-apoptotic genes have been observed in aluminium sulphate-induced neurotoxicity, "*careful attention should be paid to the neurological status and neuropathological outcome of the thousands of unfortunate victims at Camelford"* (eBMJ, 21st April 2006).

Professor Margaret Esiri is one of the country's leading neuropathologists, and Dr Chris Exley is an expert in aluminium exposure.

In December 2007, the West Somerset Coroner Michael Rose ordered the police to re-open the Camelford pollution case following allegations of a cover-up (Guardian, 13th December 2007; also reported by BBC News: http://news.bbc.co.uk/1/hi/england/cornwall/7142515.stm).

Responding to this announcement, Sue Waddle, spokesperson for the charity ME Research UK, a magistrate and the mother of a daughter severely affected by ME, wrote to The Guardian on 16th December 2007: *"I and many others await with interest the outcome of any police inquiry. A 1995 paper by two psychiatrists asserted that mass hysteria and / or anxiety were responsible for the supposed suffering of those in the Camelford area at the time. (One of these 'experts') has also given his expert opinion on many other 'non-illnesses' and 'unfounded health worries'. He happens to be the Government expert on electricity pylons, mobile phone masts, Gulf War Syndrome and myalgic encephalomyelitis. What has prompted the Coroner's call for an inquiry is irrefutable, empirical evidence from the organs of some of the victims who have died. I cannot see how psychological problems can cause the build up of enormous amounts of aluminium in the brain – much less viral infection in the spinal cord of victims of ME".*

In February 2009, following a FOIA request, it was reported that the Coroner warned Ministers of the *"serious political consequences"* of not assisting his inquiry. In a letter requesting £110,000 for further medical research, Coroner Michael Rose told Health Secretary Alan Johnson MP that he was *"fearful for the ramifications once it becomes known that the lives of thousands in Cornwall are put in jeopardy…"*. The Minister, Ben Bradshaw MP, took three months to respond to the Coroner, whose request was refused by the Department of Health. From letters released to the Western Morning News, it is known that Mr Bradshaw urged the Coroner to *"reconsider"* his (Mr Bradshaw's) request for the publication of a Government-ordered Report into the long-term health effects of the incident to be delayed but the Health Minister was not to be moved: "*We have mechanisms to fund policy-related research, but such work is commissioned by issuing a call for proposals for research to address the problem at hand and tendering. We then use peer review to commission the most appropriate and promising proposal"*. The Coroner responded: *"I do not say this lightly….but can you imagine anything more prejudicial to a Government-backed review denying that there was any health risk when the jury may be asked to accept the evidence of one of the country's leading neuropathologists* (Professor Margaret Esiri) *who may say the opposite?"* (http://www.thisisnorthdevon.co.uk/northdevonsurfing/news/Water-poison-research-needs-funding/article-664972-detail/article.html).

Clearly the medical evidence did not support David and Wessely's beliefs that the Camelford disaster was merely contagious mass hysteria, any more than it supports the Wessely School's notion that ME/CFS is

aberrant behaviour that is amenable to cognitive restructuring and exercise, a notion that the PACE Trial seems designed to support.

The MRC PACE Trial Principal Investigators

There are three PACE Trial Principal Investigators and all are mental health professionals. Why two psychiatrists (Professors Peter White and Michael Sharpe) and a behavioural therapist (Professor Trudie Chalder, a former mental nurse who works with Wessely and who is now Professor of Behavioural Psychotherapy) should be in charge of an MRC clinical trial relating to ME/CFS, a neurological disease, is -- like so much to do with this trial -- a matter open to conjecture. Professors White, Sharpe and Chalder all have fixed beliefs about patients with "CFS/ME" which remain uninfluenced by the substantial biomedical evidence that proves their beliefs to be seriously misinformed.

The Principal Investigators' insistence that no investigations should be done to define the "CFS/ME" patient population seems to reinforce the prevalent perception that they are conducting research that will deliver their intended outcome.

Professor Peter White is the PACE Trial Chief Investigator.

Peter White has long been determined to carry out such a trial: on 2nd March 1989 he wrote to Dr DA Rees, the then–Secretary of the MRC, saying: "*RESEARCH ON POST-VIRAL FATIGUE. I understand that the Medical Research Council may be considering special grant awards for research in this area. If this is the case, I would like to forewarn you that I shall be looking for funding for substantive projects to test various hypotheses regarding the physical and psychological aspects of this putative diagnosis…I will be seeking funding…(for) a treatment trial of a graduated return to physical activity and exercise".*

On 10th April 1989 Dr Katherine Levy from the MRC replied on behalf of Dr Rees, informing Peter White that he had been misinformed.

However, Peter White persisted, and the PACE Trial is the result.

Peter White seems certain that "CFS/ME" is a somatoform disorder. In his chapter on CFS in the section "Psychological Medicine" co-authored with the late Professor Anthony Clare (Kumar and Clark: "Clinical Medicine", August 2005: pp1281 *ff*), White states:

"Abnormal illness behaviour occurs when there is a discrepancy between the objective somatic pathology present and the patient's response to it…'Functional' disorders are illnesses in which there is no obvious pathology or anatomical change in an organ…The psychiatric classification of these disorders would be somatoform disorders. Examples of functional disorders (include) fibromyalgia, chronic or post-viral fatigue syndrome, multiple chemical sensitivity, irritable or functional bowel syndrome, irritable bladder syndrome.

"CFS: There has probably been more controversy over the existence and aetiology of CFS than any other functional syndrome in recent years. This is reflected in its uncertain classification as neurasthenia in the psychiatric classification and ME under neurological disorders….aetiological factors include physical inactivity…Immune and endocrine abnormalities noted in CFS may be secondary to the inactivity…The general principles of management of functional disorders (include) cognitive behaviour therapy (to challenge unhelpful beliefs and change coping strategies) and graded exercise therapy (to reduce inactivity and improve fitness). However, few patients regard themselves as cured after treatment…Outcome is worse with…the conviction that the illness is entirely physical. Perpetuating (maintaining) factors include avoidant behaviours (and) maladaptive illness beliefs".

From these beliefs of the PACE Trial's Chief Investigator, it seems unlikely that the Trial includes people with discrete ME, despite the Investigators' assertions that the PACE Trial does include them.

The Trial is using the Oxford criteria which do not define patients with ME/CFS. The Trial's *"operationalised Oxford research diagnostic criteria for CFS"* (Trial Protocol version 5, 2006, Section 7.2) were partly financed by Peter White's own money (JRSM 1991:84:118-121), which perhaps demonstrates an unusual level of personal interest in "CFS/ME".

As William Epstein makes plain, studies reporting gains from behavioural interventions relied on patient self-reports in situations that probably encouraged exaggerated reports of progress, as the studies were conducted by researchers with an apparent stake in the behavioural interventions they were evaluating (Psychotherapy as Religion [chapter 5], University of Nevada Press, Reno, Nevada, 2006).

Peter White is known for his published belief that: *"some people believe that medicine is currently travelling up a 'blind alley' (and) that this 'blind alley' is the biomedical approach to healthcare. The biomedical model assumes that ill-health and disability is directly caused by diseases and their pathological processes (but) there is an alternative approach – the biopsychosocial approach is one that incorporates thoughts, feelings, behaviour, their social context and their interactions with pathophysiology"* (Biopsychosocial Medicine. An integrated approach to understanding illness. OUP 2005. Ed. Peter White).

The book arose out of a two-day conference held at the (pharmaceutical) Novartis Foundation in London on 31st October and 1st November 2002, being a joint venture between the Novartis Foundation and a body called One-Health, said to be a not-for-profit company that (quote) "*was established in order to promote a system of healthcare based on the biopsychosocial model of ill-health*".

Peter White is Chairman of One-Health and his fellow Directors include Professor Trudie Chalder.

Many people believe that it is a retrograde step to reject the hard-earned scientific evidence -- gained over centuries -- that ill-health is directly caused by disease and its pathological processes and to retreat into the blind alley of ascribing illness to "aberrant" beliefs instead of to pathogens.

There is a long history of the biopsychosocial model of disease being discarded once the evidence is obtained that disproves it – according to one eminent NHS Consultant Clinician who specialises in ME/CFS, the psychosocial model is a default posture which some people embrace when they do not know what is going on or do not understand the science (personal communication).

In 1998 psychiatrist Niall McLaren showed that the biopsychosocial model was a mirage (A critical review of the biopsychosocial model. Australian and New Zealand Journal of Psychiatry 1998:32:8692) and in his 2002 paper he showed how reliance upon such a non-existent model is nothing but illusion (The myth of the biopsychosocial model. Australian and New Zealand Journal of Psychiatry 2002:36:5:701).

McLaren points out that psychiatrists have made a mistake in crediting Engel as author of the biopsychosocial model of disease, when Engel did not write any such model. All the model consists of is three words: "The Biopsychosocial Model".

McLaren notes that psychiatry seems to have mistaken Engel's call for a more considerate model with an assumed existence of such a model. To quote McLaren: *"Nothing (Engel) wrote constituted a coherent series of propositions that generated testable predictions relating to the unseen mechanisms by which mind and body interact, ie. a scientific model for psychiatry".*

Perhaps pertinent to the Wessely School's apparent unwillingness to heed the biomedical advances in ME/CFS, McLaren points out that: *"**preconception, bias and prejudice may determine what we see. In turn, what we see often serves to inform what we believe. By this means, science can slip into self-justification**".*

McLaren notes that some psychiatrists repeatedly invoke Engel's biopsychosocial "model" and that they accept without demur (or references) that it is a reality, when nothing could be further from the truth.

He asks: *"Why do these intelligent people, their reviewers, their editors and, above all, their readers, continue to pay homage to something that does not exist?"*

Wessely School psychiatrists, however, appear certain that their own beliefs and their reliance upon the "biopsychosocial" model are correct. They have built their careers upon it, so they must be right.

To quote McLaren: *"A Medline search of the word 'biopsychosocial' yielded nearly four hundred references, not one of them critical. Indeed, the Journal of Psychosomatics now uses the terms 'psychosomatic' and 'biopsychosocial' interchangeably.* ***In its present form (it) is so seriously flawed that its continued use in psychiatry is not justified. In a word, the officially-endorsed biopsychosocial model is pure humbug because it does not exist.***

*"Psychiatrists have long attempted to convince the general public, the funding bodies and, most significantly, the younger generations of students and psychiatrists that the profession has articulated a rational model which grants it special and unique knowledge of the aetiology of mental disorder. It is my view that we are guilty of the grossest intellectual neglect or of outright scientific fraud" (*The Biopsychosocial Model and Scientific Fraud. N McLaren. May 2004; available from the author at jockmcl@octa4.net.au *).*

McLaren is not the only psychiatrist to raise concerns about the lack of attention by certain psychiatrists to causal research. Per Dalen, a Professor of Psychiatry in Sweden, comments: *"****There is a theme that not only survives inside the medical culture in spite of an almost total lack of scientific support, but actually thrives there due to the support given by leading circles. This is the use of psychological theories as a means of reclassifying bodily symptoms as mental problems in cases where conventional medicine is at a loss for an explanation, particularly patients with so-called new diagnoses.***

"*Since I am a psychiatrist, I have for a long time been intrigued by the extraordinary use of psychiatric causal explanations for illnesses that not only go with predominantly somatic symptoms, but also lack any basic similarity to known mental disorders.*

"Today it is common to talk about somatization as if this were something that is really understood. It is supposed to be a condition with psychological causes, where looking for somatic explanations is useless (and) should be avoided, because it may make the patient even more preoccupied with bodily complaints.

"It must be noted that there is no proof that it is justified to apply the label of somatization to such conditions as chronic fatigue syndrome and several more illnesses that established medicine has so far failed to explain scientifically.

"As a psychiatrist, I have to say that it is distressing how unconcernedly certain colleagues are allowing interests other than those of the patients to take precedence, (but) only a minority of psychiatrists are involved" (http://www.art-bin.com/art/dalen_en.html).

It is curious that the Wessely School persist in their belief that they have the right to demand a level of "evidence-based" proof that ME/CFS is not an *"aberrant belief"* as they assert, when their biopsychosocial belief system that perpetuates their own aberrant belief about the nature of ME/CFS has been exposed as being nothing but a myth.

In his submission to NICE on the draft Guideline of September 2006 on "CFS/ ME", Peter White seemed to show his true beliefs about ME/ CFS patients. The draft Guideline recommended the provision of equipment and adaptations to those disabled by "CFS/ME", but White's response was clear: "*We disagree with this recommendation. Why should someone who is only moderately disabled require any such equipment? Where is the*

warning about dependence being encouraged and expectation of recovery being damaged by the message that is given in this recommendation?" (http://tinyurl.com/2fpjxc). NICE, however, rejected White's recommendation.

Despite documented concerns about his unproven beliefs, including serious concerns about his irrefutable conflicts of interest set out in November 2006 in the Report of the Gibson Inquiry by parliamentarians (see below), Peter White is lead advisor on "CFS/ME" to the Department for Work and Pensions.

In June 2004 Peter White was awarded an OBE for his work on "CFS". The citation was: "*For services to medical education"*. Notices circulating at the time proclaimed him as leading the research into CFS/ME and said his OBE was a *"well-deserved honour and acknowledgement of his contribution to work on CFS/ME".*

For someone to receive such an honour seems surprising if the person so honoured is apparently ignorant of the established facts pertaining to the subject of his research interest for which he was honoured.

Professor Michael Sharpe believes that there is no pathology in ME/CFS. He describes patients who suffer from it as *"the undeserving sick of our society and our health service"* (lecture given in October 1999 hosted by the University of Strathclyde) and asserts: *"The label of CFS avoids the connotations of pseudo-disease diagnoses such as ME"* (Occup Med 1997:47:4:217-227).

His view is that: *"It is apparent that the attitude of patients suffering from this chronic state must be changed – the knowledge that experience has shown that certain sensations have resulted from certain activities must be replaced by a conviction that these efforts may be made without harm"* (The Science of the Art of Medicine. Inaugural Lecture, University of Edinburgh, 12th May 2005, this being national ME Awareness Day). In his lecture, Sharpe spoke on how to treat diseases with *"no pathology"* (but he seems to dismiss the symptoms that are a manifestation of pathology) and he highlighted what he referred to as medicine's "*blind spot"* in dealing with symptoms that *"are not expressions of disease".*

Together with Simon Wessely, Michael Sharpe contributed chapter 5 (Chronic Fatigue and Neurasthenia) in a book entitled "Somatoform Disorders", Volume 9, edited by Mario Maj (John Wiley & Sons, Chichester, 2005). Although their chapter title refers to "Chronic Fatigue", it starts by stating: "*This chapter reviews current knowledge about chronic fatigue syndrome (CFS) and neurasthenia"*, which immediately reveals not only a telling lack of scientific rigour but also the underlying agenda of the Wessely School.

In their chapter, Sharpe and Wessely state: "*The term CFS subsumed a multitude of previous terms (which) include myalgic encephalomyelitis and post-viral fatigue syndrome, as well as neurasthenia"* (a patently untrue assertion, according to the WHO).

*"Many but not all patients with CFS can be given a psychiatric diagnosis…Where there is considerable concern about concepts such as immune dysfunction (and) viral persistence, there may be greater likelihood of symptom persistence…**CFS is a disorder of effort perception**….**The belief that activity is damaging may be a critical psychological target for effective rehabilitation".***

Given the extent of the international literature on ME/CFS, Sharpe and Wessely's pre-supposition and apparently elective lack of knowledge about the disorder seem inexplicable.

Sharpe's beliefs about ME/CFS include the following:

"*When symptoms are found not to result from 'genuine physical illness', they are often attributed to mental illness…Evidence for the superiority of new ways of thinking about and managing such patients is growing"* (BMJ:1997:315:561-562).

"These patients want a medical diagnosis for a number of reasons. First, it allows them to negotiate reduced demands and increased care from family, friends and employer (Sharpe does not consider the plight of people with ME/CFS who have no family and who have lost their friends because of the destructive impact of the disorder). ***Second, it may open the way for practical help in terms of financial and other benefits from government, employers and insurers"*** (Gen Hosp Psychiat 1998:20:335-338).

"My own view has long been that the issues around CFS/ME are the same as those surrounding the acceptance and management of (patients) who suffer conditions that are not dignified by the presence of what we call disease" (Ann Intern Med 2001:134:9:2:926-930).

"Factors such as immunological abnormalities are not of clinical value" (BMJ 2002:325:480-483).

World experts in ME/CFS have proved Sharpe to be comprehensively wrong – see below.

Professor Trudie Chalder has fixed ideas about "CFS/ME" that seem not to be informed by the biomedical evidence: "*So what is fatigue…it is a subjective symptom… best viewed on a continuum. Chronic Fatigue Syndrome… is characterised by profound, incapacitating chronic fatigue, which is unexplained by physical or mental illness…There is considerable controversy about the nature of the syndrome, i.e. whether it is best understood and managed within a medical or psychiatric framework…There is often a mismatch between patients' experience and health professionals' perspective…CFS patients have more unhelpful beliefs about experiencing and expressing negative emotions than controls…In summary* ***it appears that patients with CFS have some difficulty regulating their emotions****"* (The Importance of Psycho-social Aspects in Developing Chronic Fatigue Syndrome:
http://www.rikshospitalet.no/iKnowBase/Content/434520/Chalder-Psychosocial-aspects-of CFS.pdf).

Professor Chalder seems to believe that CBT is a cure-all. For example, she believes that CBT has a role to play in the control of diabetes: CBT "*is showing promise in more unlikely fields. Several studies have shown that it can improve the prognosis for some cancers and this week, Professor Trudie Chalder, of King's College, London, announced that it can help people with type I diabetes. Though her study has not yet been peer-reviewed or published, Professor Chalder described the results as positive"* (The Times, 15th September 2007).

Fourteen months later, the study was published in the Annals of Internal Medicine (Ann Int Med 2008:149:708-719). However, the "Summaries for Patients" in the same journal says: "*The researchers assigned patients to receive either Motivational Enhancement Therapy (MET), Motivational Enhancement Therapy plus Cognitive Behaviour Therapy (CBT), or usual care.* ***No patient received only CBT, so this study was unable to determine the effect of Cognitive Behaviour Therapy alone****".*

Professor Chalder's beliefs about "CFS/ME" are unambiguous: in 2007 the newly convened Biomedical Research Unit at the Institute of Psychiatry funded a project called "Emotional Processing in Psychosomatic Disorders". The Section of General Hospital Psychiatry at the IoP advertised for a psychology graduate to work on the project, which would "*involve working across the Section on Eating Disorders and the Chronic Fatigue Research and Treatment Unit".* The closing date for applications was 13th July 2007. The job reference was 07/R68. The advertisement said: "***The post holder will work under the immediate supervision of Professors Ulrike Schmidt (AN) and Trudie Chalder (CFS)"****.*

The study literature stated: *"The comparison with CFS will allow (researchers) to gauge whether any social cognition deficits are unique to anorexia, or reflect more global symptoms of psychiatric illness with marked physical symptoms".* So there it is in black and white: according to one of the MRC PACE Trial Principal Investigators, "CFS" is ***"a psychiatric illness with marked physical symptoms"***. Applicants were informed that: "***Aberrant emotional processing is a strong candidate as a maintaining factor for these disorders***" and the background to the project stated: "***Anorexia Nervosa (AN) and chronic fatigue syndrome (CFS) are classical psychosomatic disorders where response to social threat is expressed somatically***".

This is unequivocal: according to Chalder, chronic fatigue syndrome is a classical psychosomatic disorder.

Other IoP job advertisements for "CFS" that can be found on the website include one for a "Cognitive Behavioural Psychotherapist", accountable to Professor Trudie Chalder, which requires the applicant to possess ***"an understanding of the needs of people with mental health problems"***.

Professor Chalder's views as exemplified in those job advertisements seem to give the lie to the Wessely School's claim that they seek to avoid Cartesian dualism.

There is compelling evidence linking ME/CFS with exposure to environmental toxins, specifically to organophosphates and chemical warfare agents, demonstrating that patients with ME/CFS have reproducible alterations in gene regulation, especially those genes associated with immune, neuronal and mitochondrial function (N Kausnik, ST Holgate and JR Kerr et al. J Clin Pathol 2005:58:826-832).

Trudie Chalder, however, believes that CBT is capable of reversing these acquired alterations in gene regulation (Presentation to the Group of Scientific Research into ME at the House of Commons [the Gibson Inquiry] 7th June 2006).

She also believes that CBT can restore people with "CFS/ME" to full time employment (Occupational Aspects of the Management of Chronic Fatigue Syndrome: a National Guideline; NHS Plus, October 2006: DH Publications 2006/273539).

Professor Chalder features in the Wessely School's Training Video for Physicians ("Training Physicians in Mental Health Skills"). The video lasts 45 minutes and is presented by Professor Andre Tylee and Professor Trudie Chalder; it claims to demonstrate how not to get into arguments with the patient, how to form a therapeutic alliance with them, and how to carry out a plan of treatment aimed at the restoration of normal function.

In the video, Tylee says: *"Is it important to sort of put somebody right if they believe it's due to a virus?"* and Chalder replies:

"I mean I think it's important to incorporate that belief in a more sophisticated model of understanding the illness than you would share with the patient…. people think that there's something lurking in the cupboard as yet undiscovered that is creating the problem and of course that's I think in their mind a bit silly (sic). ***It's really important that patients keep a detailed diary of their activities so that you can then re-order all of the activities…We know the degree of pathology is not necessarily correlated with the degree of disability"***.

Professor Chalder seems to believe that patients and even their doctors can be difficult to "brain-wash" with (and about) CBT, so she seems to have a strategy to overcome such difficulties.

In "Biopsychosocial Medicine" edited by Peter White referred to above (chapter 12: Discussion: "What are the barriers to healthcare systems using a biopsychosocial approach and how might they be overcome?"), Trudie Chalder made a seemingly disturbing contribution: *"Rather than start with the physicians, which might be quite a difficult task, we could make a start with youngsters in schools. My experience is that they are much easier to educate.* ***The only barrier is the parents. Once we have the child on our side we are in a very good position"*** (http://www.meactionuk.org.uk/PROOF_POSITIVE.htm).

At the 2006 British Association for Behavioural and Cognitive Psychotherapy (BACP) Conference in Warwick, Professor Chalder gave Workshop 12 ("Beyond Simple Techniques in the Treatment of Medically Unexplained Symptoms"), at which she said: ***"The extent of the disability is usually determined by the degree of belief in the physical nature of the symptoms… We will discuss strategies that may be employed when meeting resistance in the patient…".***

Strategies that may be employed when meeting resistance have been a cause for concern, especially in the case of children, were encapsulated in a BBC Panorama documentary on psychiatric abuse of children with ME ("Sick and Tired") that was broadcast on 8th November 1999.

Dr Tony Johnson: although not a Principal Investigator, Tony Johnson PhD, Deputy Director of the MRC Biostatistical Unit (BSU) at Cambridge, plays an important role in the PACE Trial. He is a member of both the Trial Management Group and the Trial Steering Committee.

The Trial Identifier states at section 4.1: "*The Trial co-ordinator…will liaise regularly with staff at the Clinical Trials Unit (CTU) who themselves will be primarily responsible for randomisation and database design and management (overseen by the centre statistician Dr Tony Johnson) directed by Professor Simon Wessely"* and at section 4.4: "*Prof Simon Wessely will oversee the CTU (Clinical Trial Unit), with the support of Dr Tony Johnson….".*

Ten individual reports constitute the BSU's Quinquennial Review for the years 2001 to 2006 and include one by Tony Johnson.

One part of the Quinquennial Review that is relevant to the PACE Trial states: "***The Unit's scientists 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 was elaborated upon by Johnson himself in his own Report within the Review and he referred to the fact that the PACE and FINE Trials were funded by the MRC "*despite active campaigns to halt them"*.

His Report was a substantial document in which he made allegations about the ME/CFS community that, when challenged, he was unable to substantiate. Coming from such a senior figure within the MRC, and considering his level of involvement with the PACE trial, his adverse comments about "CFS", the ME/CFS community and those who support them would have carried considerable authority and influence.

Appendix I provides detailed information about Dr Johnson, as his involvement in the PACE trials merits closer scrutiny.

He has collaborated with Professors White, Wessely, Sharpe and Chalder (his BSU Report on "Chronic Fatigue Syndrome" was written with Peter White, Trudie Chalder and Michael Sharpe) so his neutrality in relation to ME/CFS may be open to question.

From Johnson's BSU Quinquennial Report for the years 2001 to 2006, the ME/CFS community was left in no doubt about the bitter contempt for sufferers, for some charities (which were far from "*more extreme*", being the ME Association and The 25%ME Group for the Severely Affected), and for those MPs who support them that seems to exist at the MRC, or that the seam of Wessely School dismissal and denigration of ME/CFS patients does indeed seem to run deep.

Flawed studies

The MRC PACE Trial seems to be predicated on the alleged efficacy of the Wessely School's previous studies of CBT/GET on "CFS/ME" patients: based on the their own previous studies of "CFS", the Chief Investigator (Peter White) provided predictions of positive outcomes for patients receiving either CBT or GET **before the PACE Trial even commenced** (Trial Identifier, section 3.12).

Those studies, however, have been stringently and repeatedly criticised in the medical literature as being methodologically flawed.

The only issue for the Wessely School seems to be how to achieve the implementation of CBT/GET for the whole range of "medically unexplained fatigue" – into which the Wessely School have incorrectly subsumed ME -- throughout the nation and beyond, including the United States and New Zealand.

It is a matter of record that when serious errors and misrepresentations in Wessely's published articles have been pointed out to him and to Editors (which, when challenged, even Wessely himself cannot rationally condone), he blames his peer-reviewers.

One instance of this occurred in 1997 in relation to his article in the Quarterly Journal of Medicine (The prognosis of chronic fatigue and chronic fatigue syndrome: a systematic review. Joyce J, Hotopf M, Wessely S. Q J Med 1997:90:223-233), the many flaws of which were exposed by research methodologist Dr Terry Hedrick in an analysis that was subsequently published (Q J Med 1997:90:723-725). To quote Hedrick: *"Not only did the article fail to summarize the psychiatric literature accurately, it omitted discussion of the many avenues now being explored on the organic underpinnings of (ME)CFS"*. Following Hedrick's exposure to the Editor, Wessely blamed his peer-reviewers for allowing his mistakes to go unnoticed (personal communication).

This is not an isolated example of Wessely blaming his peer-reviewers. There have been others, for example, when UK medical statistician Professor Martin Bland, then at St George's Hospital Medical School, London, pointed out significant statistical errors in a paper by Wessely and Trudie Chalder, saying that Wessely's findings were "*clearly impossible"*, Wessely absolved himself from any blame, but Bland was robust: "*Potentially incorrect conclusions, based on faulty analysis, should not be allowed to remain in the literature to be cited uncritically by others"* (Fatigue and psychological distress. BMJ: 19th February 2000:320:515-516). Wessely was compelled to acknowledge on published record that his figures were incorrect: "*We have been attacked by gremlins. We find it hard to believe that the usually infallible statistical reviewers at the BMJ could have overlooked this and wonder, totally ungallantly, if we can transfer the blame to the production side".*

Published criticism of the Wessely School's studies on "CFS/ME" is readily accessible for all to read, particularly for:

- the use of a heterogeneous patient population (studies using mixed populations are not useful unless researchers disaggregate their findings)

- selective manipulation of others' work, claiming it supports their own findings when such is not the case (for example, in the 1996 Joint Royal Colleges Report CR54, Wessely et al mention a paper by Bombardier and Buchwald [Arch Intern Med 1995:155:2105-2110] and convey that it supports their own stance, whereas the paper actually states: "*The fact that the same prognostic indicators were not valid for the group with CFS challenges the assumption that previous outcome research on chronic fatigue is generalisable to patients with chronic fatigue syndrome";* Wessely et al also mention a paper by Sandman [Biol Psych 1993:33:618-623] in apparent support of their own view that the results of neuropsychological testing have been *"inconsistent"*, but the paper itself concludes: "*the performance of the CFIDS patients was sevenfold worse than either the control or depressed group. These results indicate that the memory deficit in CFIDS was more severe than assumed by CDC criteria. A pattern emerged of brain behaviour relationships supporting neurological compromise in CFS"*

- their focus on the single symptom of "fatigue" whilst ignoring other significant signs and symptoms associated with the cardiovascular, respiratory, neurological, endocrine and immunological systems

- generating conclusions before generating the data to support such conclusions, for example, in his paper on the status of vitamin B in CFS patients (JRSM 1999:92:183-185), Wessely found a

functional deficiency of the B vitamins, particularly pyridoxine, but also of riboflavin and thiamine. The study involved only 12 patients, yet the conclusion states: *"But clearly, many patients with CFS are currently taking vitamin and other supplements with little evidence of benefit"*. If the study involved only twelve patients, to conclude that "*many*" patients show *"little evidence of benefit"* from taking supplements is remarkable, but it does concur with section 9.20 of the 1996 Joint Royal Colleges' Report (CR54), which states: "*We have concerns about the use of complementary therapy and dietary interventions"*, a statement that is in accordance with the published views of HealthWatch, of which Wessely is a*"leading member of the campaign"* (see below)

- advising Government bodies that the reported biomedical abnormalities *"should not deflect the clinician away from the biopsychosocial approach and should not focus attention towards a search for an 'organic' cause"*, and for their recommendation that no advanced tests should be carried out on "CFS/ME" patients when it is those very tests that reveal the unequivocally organic nature of the disorder (Joint Royal Colleges' Report 1996: CR54).

When the Centre for Reviews and Dissemination (CRD) at the University of York produced its 2005 Systematic Review of "evidence-based" (mostly Wessely School) studies on behavioural interventions for ME/CFS that was commissioned to support the 2007 NICE Clinical Guideline 53, there was much concern throughout the ME/CFS community, not least because some of the studies had used the Oxford criteria which, by definition, excluded those with ME.

The 2005 Systematic Review was an update by Bagnall et al of the CRD's own 2001 Systematic Review by Whiting and Bagnall et al (JAMA 2001:286:11:1360-1368). The 2005 Systematic Review was exposed in a comprehensive analysis by Hooper and Reid as a travesty that many people believed amounted to research misconduct (http://www.meactionuk.org.uk/FINAL_on_NICE_for_Gibson.html).

Hooper and Reid pointed out that the Bagnall et al (York) Review cited the same Wessely School papers as in their first (2001 JAMA) review but with a significant difference: virtually all the negative comments about CBT/GET that had appeared in 2001 in JAMA had been removed from the 2005 up-dated review.

This meant that the same team's negative comments about methodological inadequacy, withdrawal rates, drop-out rates, unacceptability of treatments and the exclusion of severely affected patients were omitted from their up-dated review, as were their previous observations which recorded that (i) improvements might be illusory, (ii) there was no objective evidence of improvement, (iii) there was little lasting benefit from CBT, and (iv) the data in the Wessely School studies relied upon had been corrupted. Furthermore, previous reports of adverse events were excluded, as was the fact that follow-up revealed relapse after the interventions.

Despite the acknowledgement by the 2001 team of the paucity of good quality evidence to support the recommendations of CBT/GET, none of these previous observations was mentioned in the 2005 up-date for NICE. All negative comment, no matter how eminent the source, was simply removed to the extent that it seemed inescapable that Bagnall et al had been subjected to covert external influence. As Hooper and Reid noted: "*It would be most unfortunate if a powerful outside influence has been able to impose his own concepts on a team of supposedly neutral reviewers*".

Even more disturbingly, not only had those caveats disappeared from the 2005 version, but citation of the JAMA 2001 article in which they had appeared was also deleted. In 2001 Bagnall's work appeared in one of the world's most prestigious medical journals (JAMA) but in 2005 she disowned her own 2001 work and there is abundant evidence that in 2005 Bagnall was prevailed upon to dilute or delete opinions she held in 2001, a matter that some considered to be research misconduct. What rationale could possibly underlie this astonishing self-censorship?

The answer may be found in the fact that the team advising the Bagnall (non-medical) review team at York was led by Professor Simon Wessely, whose own data-base was originally provided for the CRD team, a fact confirmed by the UK's Chief Medical Officer in a personal communication in September 1999.

Having serious concerns about both the PACE and FINE Trials and the Wessely School studies upon which they relied, in October 2004 David Sampson, a psychopharmacologist / neurophysiologist and Tutor in experimental design and statistical analysis (a previous recipient of an MRC grant for his research into neuropharmacology), submitted a formal complaint to the MRC in which he said:

"*I am appalled to have to bring to the attention of the MRC that it would appear that both* ***massage of diagnostic criteria and experimental protocol…*** *appears to be taking place in two areas of research into CFS/ME. These are not allegations to be taken lightly and I expect the MRC to launch an immediate investigation".*

Referring to the MRC's own 2003 Research Advisory Group's Report (CFS/ME Research Strategy; 1st May 2003), Sampson's complaint mentioned that he *"noted that the panel which formed the basis of your report consisted of at least three members who have worked or have been connected with the Cognitive Behavioural Treatment group at King's and who plainly condone their CBT policy….The Whiting Review consisted chiefly of studies into CBT (and the Review) panel were 'helped in interpreting these studies by an expert in the field of CFS/ME' who was responsible for publishing most of the research that they were supposedly reviewing. This I found astounding".*

David Sampson's complaint to the MRC was not addressed; he was informed by Elizabeth Mitchell (well-known to the UK ME/CFS community) effectively that the MRC was not interested in his complaint.

It is perhaps worth noting that during the life of the MRC's Research Advisory Group (RAG) on CFS/ME in 2002 - 2003, a significant amount of fully referenced documentation about the biomedical nature of ME/CFS was submitted – some of it by Recorded Delivery -- to Elizabeth Mitchell at the MRC but was unacknowledged and wholly ignored.

Since the MRC was not willing to investigate his complaint, at the All Party Parliamentary Group on ME (APPGME) on 22nd January 2008 a pre-publication copy of David Sampson's analysis of Peter White's 2001 paper in the Lancet (2001:358:9297:1946-1953) was put into the hands of the Health Minister in person, who promised to look into the issues it contained (ie. evidence that Peter White's 2001 study was flawed and that his conclusions about the benefit of CBT/GET were not supported by his own data).

Nothing came of the Minister's personal promise. The Minister in question was Ann Keen MP, who was Parliamentary Under Secretary of State for Health. It is the case that in June 2009, in The Daily Telegraph's "Complete Expenses Files" that documented the expenses claims of elected Members of Parliament, Ann Keen and her husband were dubbed "Mr and Mrs Expenses", with the comment: "*the husband and wife MPs claimed almost £40,000* ***a year*** *on a central London flat although their family home was less than ten miles away".*

Not only did nothing come of the Minister's promise but, although accepted by the Journal of Chronic Fatigue Syndrome, David Sampson's paper was never published because the Journal ceased publication and was bought by Psychology Press (the Taylor and Francis Group).

Neither did anything come of the Gibson Inquiry's Report (see below) that in 2006 called for an inquiry into the vested interests of the Wessely School (and of Peter White in particular), about which Jane Spencer from the Department of Health recently wrote: "*The Department of Health was not involved in producing that report, and has no plans to respond to its findings"*
(http://www.facebook.com/edittopic.php?uid=154801179671&topic=10499&action=4#/topic.php?uid=154801179671&topic=10550).

Wessely School members have long been charged with misusing science to support their particular bias.

For example, in 2003, in the spirit of correcting misinformation Dr Linda Goodloe, a biopsychologist, commented on a paper that was co-authored by Trudie Chalder (Illness perceptions and levels of disability in patients with chronic fatigue syndrome and rheumatoid arthritis. R. Moss-Morris et al. J Psychosom Res 2003:55:4:305-308): ***"This study is an exceptional example of misusing science to support a particular bias****…Biased assumptions permeate both the design and interpretation of data of this study…The bias is not subtle and appears in every step of the analysis. However the main fault is in the design of the experiment. To even begin to discuss differences in 'perceived disability' between groups, the authors would have to find some way of controlling for any symptom differences, and this study doesn't even mention that there ARE any symptom differences, much less factoring them into the design. Symptom differences between these groups is such a huge source of error that it makes using these differences to make inferences about psychological states bizarre.* ***There is nothing in the design of the experiment or the data to justify even floating the suggestion that the perceptions of the (ME)CFS group are less valid or less grounded in reality than those of the RA group.*** *The authors ignored the large body of knowledge, the documented findings of irregularities in assorted (immunological, neurological, hormonal, gastrointestinal etc) systems in those with (ME)CFS that are not shared with RA subjects. However, the bottom line is that even without the biased interpretations, the methodology doesn't meet even the most minimally acceptable standards"* (Co-Cure ACT: 23rd September 2003).

Other illustrations include the following:

The study by Sue Butler, Trudie Chalder, Maria Ron and Simon Wessely (JNNP: 1991:54:153-158) was remarkable for its inexplicably high refusal and drop-out rates, lack of a control group and no independent assessment of outcome; it was criticised in a Cochrane Review on CBT for CFS (2000: issue 4) for its poor scientific quality and for not excluding medical causes of fatigue; furthermore the design failed to permit the effects of concurrent antidepressant therapy to be satisfactorily distinguished from purely psychological treatments (with grateful acknowledgement to David Sampson and to Dr Charles Shepherd for the analysis which was taken from his book "Living with ME").

The above study would be of little interest were it not for the fact that in the original study there was an unacceptably high refusal and drop-out rate, whilst an almost identical study published in 1997 by the same authors showed these rates to be much lower (American Journal of Psychiatry 1997:154:408-414).

In this 1997 study of 60 patients, half received CBT in the form of *"graded activity and cognitive restructuring"* and half received "*relaxation*". The authors stated: *"CBT is used to modify behaviours and beliefs that may maintain disability and symptoms"*. Three subjects withdrew from the CBT group and four withdrew from the relaxation group. The authors stated that at final follow-up (six months after the course of CBT and relaxation completed), 19 patients *"achieved good outcomes compared with 5 patients in the relaxation group"*. Somatisation disorder and severe depression were cited as exclusion criteria; nine participants, however, were described as having 'major depression' and there were high levels of existing psychiatric morbidity in the study cohort. Outcome measures were said to relate to "*subjectively experienced fatigue and mood disturbance, which are the areas of interest in chronic fatigue syndrome"*. This statement alone indicates that the study cannot have been considering people with ME/CFS because neither "fatigue" (or "tiredness") nor mood disturbance is a defining feature of ME/CFS (the defining feature of ME/CFS being post-exertional muscle fatigability with malaise).

Of concern is the fact that the authors stated: *"The aim was to show patients that activity could be increased steadily and safely without exacerbating symptoms"*. That is a remarkable statement. It demonstrates that the authors had decided -- in advance of the outcome -- that activity could be increased without exacerbating symptoms. This is not merely the authors' hypothesis: that this will be the outcome is taken for granted. Of note is the fact that the outcome did not meet the authors' certainty, and the authors had to concede that: "*cognitive behaviour therapy was not uniformly effective: a proportion of patients remained fatigued and symptomatic"*. Perhaps for this reason, the presentation of results was mostly reported as averages, rather

than giving actual numbers of patients. The authors acknowledged that: "*The data from all the outcome measures were skewed and not normally distributed, with varying distributions at each measurement point"*. In such circumstances, merely providing "average" figures is not the most appropriate illustration of findings. In summary, this RCT has little relevance in general and none whatever to people with ME/CFS (with grateful acknowledgement to ScotME for this analysis).

In 2001, Trudie Chalder and Simon Wessely et al published their 5-year follow-up of their 1997 paper (Am J Psychiat 2001:158:2038-2042). The original 1997 study had 60 patients, whilst the 2001 follow-up study had 53 patients. Significantly, this study suffered from corrupt data: the authors themselves stated: *"56% of the patients undergoing CBT reported receiving further treatments for their chronic fatigue symptoms; other treatments used were antidepressants, counselling, physiotherapy and complementary medicine"*. Over the course of the five year follow-up, treatment of many patients had deviated from the trial protocol, rendering the outcome measures meaningless.

It is worth noting that in the NICE Guideline (CG53, 2007) that recommended CBT for "CFS/ME", ten studies were identified (including the two mentioned above) and in most of the ten identified trials of CBT the methodology does not meet even the most minimally acceptable standards. **Five out of the ten trials registered no overall effect**, yet the Guideline states on page 198: "*Eight of the studies reported beneficial effects of CBT"*, which seems to indicate a determination on the part of those advising NICE to use CBT whatever the evidence.

Three studies in particular by two of the PACE Trial Principal Investigators deserve attention (the Fulcher and White study of 1997; the Sharpe et al study of 1996 and the White et al study of 2001).

The Fulcher and White study (BMJ 1997:314:1647-1652) specifically states: "*If patients complained of increased fatigue they were advised to continue at the same level of exercise"*, which should be borne in mind when noting that the PACE Trial literature states that the undeniable adverse effects of previous GET interventions were likely to be due to improperly administered therapy (see below).

It is notable that at least 40% of White's participants were working at the time of the study; all were capable of at least 15 minutes of intense aerobic activity, and 30% of patients enrolled were receiving concurrent antidepressant therapy or hypnotic medication, yet the authors stated that patients with psychiatric disorders were intentionally excluded.

As Mike Sadler, Consultant in public health medicine, commented in the BMJ: "*Fulcher and White conclude that their findings support the use of graded exercise in the management of CFS…Given that this is already a subgroup selected by their referral to psychiatric outpatient departments, to select out those with a current psychiatric disorder makes them an unusual group indeed"* (BMJ 1997:315:947-948).

There is evidence that Peter White is fully aware that his 1997 study did not look at people with ME/CFS. That study excluded people with sleep disturbance, which means that they excluded people with ME/CFS, since a diagnostic feature of ME/CFS is sleep disturbance. When this anomaly was pointed out in person to Professor White by a senior NHS Consultant Physician, Professor White shrugged his shoulders and said: (*verbatim): "So what?"*. This response by Professor White must surely cast doubt on his credibility and upon the value of the RCT in question as being "the best available evidence".

Equally, the Sharpe et al study of 1996 merits comment (BMJ 1996:312:22-26). This was a small study of just 60 patients, of which only 30 patients received CBT (the other 30 being controls). Sharpe et al concluded: "*CBT was both acceptable and more effective than medical care alone (but) few patients reported complete resolution of symptoms and not all improved".*

At the time, the study received much media publicity, with inflated claims of success. When countered by informed ME/CFS patients, The Independent published a hostile article by Rob Stepney (26th March 1996)

attacking ungrateful patients: "*Many sufferers are bitterly opposed to (CBT), arguing that their condition is physical, not psychological.* ***'Many patients have a personality which hinders recovery'.*** ***'ME is an escape route for the middle classes' claimed one psychiatrist".*** What was not made public was the fact that Rob Stepney's wife was one of the Oxford therapists involved with the trial.

On 30th March 1996 The Independent published a letter from a trial participant (Catherine Rye): *"I am a sufferer and participated in the trial. The article implies that a new successful treatment has been found for ME but that sufferers do not want to accept it. There are facts about the trial that throw into doubt how successful it is.* ***It is stated that patients in the control group received standard medical care. I was in that group but I received nothing.*** *Patients who 'improved significantly' only increased their score from 70 to 80 on a scale of general functional ability".*

Despite having to acknowledge the fact that few patients reported resolution of symptoms, the authors nevertheless asserted: "*The results show that a return to normal functioning is possible in most cases. We believe that our results have important implications for the management of patients with chronic disabling fatigue".*

Once again, Wessely School psychiatrists seemed determined to confuse chronic disabling fatigue with ME/CFS. The ME Association's Medical Advisor wrote on 18th January 1996 in The Times: "*Although 22 patients out of 30 in the Oxford trial of CBT achieved an improvement of approximately 10% in their disability rating after a year, the only other two controlled trials of CBT to be published found no benefit from this fashionable form of short-term psychotherapy. The ME Association believes that the results so far obtained do need to be viewed with a considerable degree of caution".*

Notwithstanding, the Sharpe et al study forms the "best practice evidence-base" for NICE's recommendation of CBT for all patients with "CFS/ME" in the UK, including those with ME/CFS.

Another of the PACE Trial Chief Investigator's studies merits consideration (Lancet 2001:358:9297:1946-1953). This study calls into question the validity of the broad-based definitions such as the Oxford criteria, largely because the Oxford criteria include patients with mood disorders, which makes any conclusions about ME/CFS *per se* virtually impossible.

In White's 2001 study, fatigue syndromes were classified into three groups and participants were selected according to (i) White's own empirically defined fatigue syndrome (Psychological Medicine 1995:25(5):917-924), (ii) the Oxford criteria and (iii) the CDC 1994 Fukuda criteria.

White et al had hypothesised that a previous psychiatric history and/or social adversity would predict all three definitions of fatigue syndromes on the basis of the "psychosomatic" model of "CFS/ME", but he found that neither univariate nor logistic regression analyses supported his hypothesis and that the strongest predictor for developing a fatigue syndrome following infectious mononucleosis was a positive Monospot result (ie. evidence of infection).

However, White concluded that the most likely explanation for the lack of correlation between previous psychiatric morbidity and an empirically defined fatigue syndrome was: "*that we studied participants in the first six months of their illness, whereas most previous studies observed patients several years after onset….This explanation would fit in with the hypothesis that psychosocial factors are unimportant in a fatigue syndrome of several months duration but may become more important with time".*

White's explanation, however, is not supported by his data.

White ignored one critical fact: all his fitness measurements were made <u>after</u> diagnosis, so he could have had no idea of how fit (or how deconditioned) participants were before they became ill, since patients may become deconditioned when they develop a fatigue syndrome, but this does not mean that such

deconditioning caused their illness – it may be the result of the illness, and this very study supports such a hypothesis.

If fatigue is perpetuated by deconditioning, one would expect that an activity programme that increases performance in ME/CFS would increase fitness, but the Fulcher and White (1997) study had already demonstrated no such relationship.

Of note is the fact that in his 2001 study, White made an "*adjustment*" to the data sets, stating:

"*Because there were only 16 cases of empirical fatigue at 6 months, we added 26 cases of 'fatigue not otherwise specified'…Similarly, we added the 18 cases of 'idiopathic chronic fatigue' to the 17 cases of CFS according to the CDC found at 6 months. These two categories defined participants with prolonged unexplained abnormal fatigue, but with insufficient accompanying symptoms or disability to qualify for the full syndrome*".

Most crucially, idiopathic chronic fatigue is classified as a psychiatric illness in ICD-10 at F48; similarly, it is likely that "*fatigue not otherwise specified*" will contain people with psychogenic fatigue.

Such statistical adjustment clearly distorts the data, as it increases the values for psychosocial factors.

White continues to argue that both CBT and GET are effective treatments for ME/CFS and his work is viewed as providing important evidence for this view, but the suggestion that GET can help post-infectious ME/CFS is not supported by White's own data.

In summary, the evidence for the beneficial effect of GET in ME/CFS is not persuasive: if a sample of ME/CFS patients contains a large number of patients with purely psychiatric reasons for their fatigue, then it is hardly surprising to find that psychosocial factors are important – this is tautology and reveals little about ME/CFS (with grateful acknowledgement to David Sampson for his analysis).

The above examples are merely illustrative of flawed methodology in Wessely School studies of "CFS/ME".

International criticism by experienced ME/CFS researchers / clinicians has not abated, for example the Preface to the book "Tuning The Brain" (Jay Goldstein MD; Haworth Press Inc., 2004) does not beat about the bush: "*I must say that the British CFS researchers (with very few exceptions), don't know they don't know and wouldn't care if they did. They seem to regard cognitive behavioural therapy as the Holy Grail of CFS*".

On 19th June 2009 Dr Derek Enlander from New York was critical of psychiatrists who believe that graded exercise therapy and cognitive therapy can be effective treatment. "*We have found that graded exercise therapy can actually be detrimental to the patient's progress; it can actually produce relapse. Yet this is proclaimed by several psychiatric experts to be the only mode of treatment*," he told IMT (Irish Medical Times). "*This is very, very damaging*".

It cannot be overlooked that the three PACE Trial Principal Investigators all work for the insurance industry.

Dr Jean Lennane, a psychiatrist, is outspoken about psychiatrists who work for the insurance industry:

"There are hired guns in other medical specialties, but they appear to be most frequent, and most vicious, in psychiatry – probably because, as a 'soft' science, lacking the hard evidence of X-rays and tissue examination, psychiatry is more open to opinions, no matter how outrageous"
(http://www.uow.edu.au/arts/sts/bmartin/dissent/documents/Lennane_battered.html).

The MRC's secret files on ME/CFS

It is unknown whether or not the refusal of the MRC to investigate David Sampson's legitimate complaint has anything to do with the fact that the MRC has a secret file on ME that contains records and correspondence since at least 1988 which, co-incidentally, is about the time that Simon Wessely began to deny the existence of ME. The file is held in the UK Government National Archives at Kew (formerly known as the Public Record Office) and was understood to be closed until 2023, but this closed period has been extended until 2071, at the end of which most people currently suffering from ME will be conveniently dead http://www.nationalarchives.gov.uk/catalogue/displaycataloguedetails.asp?CATLN=7&CATID=-5475665 As one puzzled ME sufferer recently noted: "*why on earth have a 73 year embargo on these documents on an illness where a load of neurotic people, mostly women, wrongly think they are physically ill?"* (http://health.groups.yahoo.com/group/MEActionUK/ 14th October 2009).

The MRC's secret files on ME/CFS are closed (ie. unavailable to the public) for an unusually lengthy period of 83 years. The standard closure period is 30 years but, as in the case of these files on ME/CFS, the standard closure period may be extended.

The 30-year rule usually applies to documents that are exempt from release under a Freedom of Information Act (FOIA) request and include, for example, documents concerning the formulation of government policy, documents related to defence, to national security, to the economy, and documents that are considered very confidential.

It may be recalled that during the life of the Chief Medical Officer's Working Group on ME/CFS (1998-2002), lay members were ordered not to discuss the deliberations and were even threatened with the Official Secrets Act, for which no explanation was proffered. A letter dated 16th June 2000 from Mrs Helen Wiggins at the Department of Health NHS Executive Headquarters in Leeds was sent to lay members of the Working Group; this letter stressed that it had become increasingly important that any documents or information, in whole or in part, that might contribute to the report must be kept confidential and to this end, members of the Working Group might be compelled to sign the Official Secrets Act. This was followed up by a letter dated 23rd October 2000 from Lord Hunt of Kings Heath, then Parliamentary Under Secretary of State at the Department of Health (ref: POH (6) 5380/83), confirming that the information held by the Working Group might in certain circumstances indeed be covered by the Official Secrets Act.

If the psychiatric lobby which dominated that Working Group was so confident that they were correct about ME/CFS, why the need to force the suppression of opposing views by resorting to threats of prosecution under the Official Secrets Act in a Working Group that had nothing to do with State security but was supposed to be acting simply in the best interests of sick people? This was in marked contrast to the "Key working principles" set out in the first Briefing Note of March 1999, which stated: "*The Group must have maximum 'transparency' ie. as much information about its activities to be distributed as possible to all potential interested parties".*

One can but wonder how the consideration of ME/CFS could rank as a state secret and of what, precisely, was the Department of Health so afraid that it even considered the use of such draconian powers? For the record, Mrs Wiggins was replaced by Robert Harkins and it was he who sent the letter dated 25th May 2004 (ref: TO1056746) in which he stated that the then new centres for CFS *"will be headed up exclusively by psychiatrists*", which was deemed to be more evidence of Government "policy" on "CFS/ME".

People wishing to access documents archived at Kew are able to make an application to access documents that are not redacted or closed, but the procedure is lengthy. Prior notification and advance booking are required; people must remove their coats / jackets and leave them, together with personal possessions including handbags, in a locker with a see-through door for which a numbered key is provided; proof of identity is mandatory and every person is newly photographed on arrival.

Legitimate access has been obtained to some of these archived documents about ME/CFS and they make interesting reading, for example:

On 1st June 1988, Dr Katherine Levy of the MRC (the same Katherine Levy referred to above who was to write to Dr Peter White on 10th April 1989) sent an internal memo: "*I have got caught up in an enquiry from HORIZON on MRC support for myalgic encephalomyelitis. Mrs Currie* (Edwina Currie MP) *is on record…as saying the MRC is supporting nothing…I had a preliminary word with the producer…she evidently wants to quote us and…I do not want us quoted as saying we think we have nothing….**They would make a meal of it!***". Handwritten comments state: "*Is this not the Royal Free Hospital Syndrome and perhaps of controversial status as a disease entity?*". The handwritten comments continue: "*I have also spoken to Dr Swash* (believed to be a member of the MRC Neurosciences and Mental Health Board), *who is among the agnostics along with… Peter Thomas* (believed to be Wessely's co-author the late Dr PK Thomas, a neurologist who is on record as describing ME patients' muscle weakness as *'simulated'* in Recent Advances in Clinical Neurology, 1990: pp 85-131) *and others: his view is that no research of any significance is being undertaken on this topic in the UK…*". On 6th June 1988, a *post scriptum* was added: "***PS I got away with no mention of Radda, the Unit, or Oxford***" (in 1984, Professor Sir George Radda, as he later became when appointed Chief Executive of the MRC in 1996, had published research using nuclear magnetic imaging that confirmed a unique biochemical defect in the way energy was being produced in an ME patient – Lancet 23rd June 1984: 1367-1369).

Another document that has been obtained through legal means is a summary of the CIBA Foundation (in 1996, CIBA became Novartis) Symposium on CFS that was held on 12-14th May 1992 (reference S 1528/1). The letter "S" indicates that the document is categorised as "Scientific" and the following quotations come from the section entitled "HIGHLIGHTS":

"*Ned Shorter* (ie. Edward Shorter, the Hannah Professor in the History of Medicine at the University of Toronto, a well-known disbeliever in ME/CFS) *fascinated the audience with his historical perspective on how symptoms of disease without apparent organic illness vary over time…Why is chronic fatigue* (sic) *so appealing to patients and their doctors? One factor must be that fatigue is difficult to disprove.* ***There is a desire among patients and doctors to upgrade their symptoms in order to stay abreast of science. Virology and immunology are dynamic, progressive branches of science, and patients are irresistibly* (sic) *drawn to them in order to explain the mysterious origin of their symptoms. This is evidence of a somatization disorder, in which patients believe their symptoms, which are psychogenic in origin, are evidence of organic disease…".***

The section on Epidemiology states: "***CFS…is a collection of symptoms, not a disease***".

The section on "Muscle fatigue" records: "*Edwards* (ie. Professor Richard Edwards from Liverpool, on record as stating: *"Many of the biochemical changes during exercise and many of the symptoms of these patients could be a consequence of their reduced habitual activities"* -- Ergonomics 1988:31:11:1519-1527) *concluded that on physiological and pathological grounds, CFS is not a myopathy;* ***a primary role for psychological / psychiatric factors was deduced from a formal comparison between CFS and myopathy patients***".

The section on Virology states: *"The meeting concluded that exhaustive analysis had failed to prove that CFS is caused by a virus or viruses (and)* ***members were increasingly drawn to the idea that the search for a single identifiable cause of CFS is meaningless…"***

The section on Psychiatry states: "*Studies have shown that the relative risk of psychiatric disorder is increased 2-6 fold in CFS cases compared to controls with physical diseases. Various themes emerged. One is of a subcortical dysfunction analogous to the cognitive problems seen in illnesses such as Parkinson's disease. The most impressive evidence of CNS disturbance was quoted by Wessely (Institute of Psychiatry) as coming from neuroendocrinological studies, suggesting a role for hypothalamic disorder as a final common pathway for CFS"* (yet Wessely still maintains that "CFS/ME" is a somatisation disorder).

The Psychiatry section continues: "*Sharpe (Oxford)* (ie. Michael Sharpe, one of the three PACE Trial PIs) *described a trial of cognitive and behavioural therapy which he is just starting at the Warneford Hospital. The aim is to help patients re-evaluate and, if appropriate, change, unhelpful feelings about their performance and symptoms, and thus break the vicious circle.* ***He admitted that the trial was a purely pragmatic approach without theoretical foundation****"* (it is interesting to see confirmation in an MRC document – and from Sharpe himself -- that this study [BMJ 1996:312:22-26], one of the most-relied upon in the "evidence-base" for CBT in the 2007 NICE Clinical Guideline, was merely pragmatic and without theoretical foundation).

The section titled "The Treatment Process" is particularly notable: "***The first duty of the doctor is to support as much useful function as possible and avoid the legitimisation of symptoms and reinforcement of disability".***

The Section "General discussion" records: "***Shorter felt that from a historical perspective, CFS was an example of a disordered mind/body relationship that would not survive****…It was important to step back and look at the whole phenomenon of somatization".*

"Summarising, ***the Chairman (Kleinman) predicted that in 10 years time…the central issues in the CFS field would be social rather than medical or scientific, partly driven by the economics and funding of the disability systems in various countries****".*

Here, again, is evidence that the problem of ME/ CFS is seen in terms of economic costs to the nation and not in terms of alleviating suffering.

Numerous sections of this document are redacted and censored under FOI exemption 40 (2) and are marked "CLOSED UNTIL 2071".

Section 40 (2) of the Freedom of Information Act usually relates to the protection of personal information; this being so, a perfectly straightforward telephone inquiry was recently made to the National Archives at Kew with a view to establishing why so many sections of a report of a scientific conference should be deemed to be "personal information" and thus closed to the public. Having been advised by staff at Kew to speak to their own FOI department with this query, the questioner duly requested to be transferred to that department, but when the subject of the query was known, there was a long delay before the questioner was put through, not to the FOI department as advised and requested, but to a female member of staff who seemed very agitated and who said that she dealt with these particular enquiries. The questioner was barely permitted to get a word in and was constantly interrupted by this member of staff, who seemed to be reading at great speed from a prepared text. When the questioner was finally able to ask why a report of a scientific meeting should be deemed to contain personal information, the result was a further lecture about how important it is to protect personal information. No explanation was provided in answer to the question posed, even when it was pointed out that personal information in the form of names of presenters at the symposium had not been redacted.

Given the unconvincing sermon on the need to protect "personal information", it is notable that other documents in the MRC file held at the National Archives make no attempt to do so, for example, on 14th February 1997, Karen Finney of the MRC sent a memo to Dr Bryant and Dr Coriat at the MRC, in which she wrote: "*Chronic fatigue syndrome (CFS) and Mr Paul Hulme* (sic). *On 15th January 1997 a query concerning MRC support for ME was referred to me…I agreed to speak to the member of the public, Mr Paul Hulme (*giving his address and ex-directory telephone number, personal information which was not redacted and is thus available to any member of the public who makes an application to see the document in question)*…Mr Hulme wished to know if MRC was funding any specific work on ME/CFS…In reply, I said I thought the MRC did not receive many proposals on ME/CFS…However, Mr Hulme was aware of a study supported by MRC and carried out at the Institute of Psychiatry. He was not happy with the fact that MRC had supported this work because ME* ***'was a real illness and not all in our mind'****….Following my telephone conversation, I asked Mr Goldstein (CAG) to run a search for applications on CFS/ME that we had received over the last year, funded or declined….Mr*

*Goldstein's search took a little while due to other pressing matters…Between 15/1 and 7/2 Mr Hulme rang on average twice a week to ask about progress. When Mr Hulme rang on 7/2 I let him know, in general terms…that during 1996 we had received four applications which had been declined on scientific grounds…Mr Hulme requested that I put the result of the search in writing…**I am aware that the follow-up letter requires careful drafting**…Mr Hulme telephoned again on 13/2 to say that he needed my letter urgently (as) he intended to fax a letter to Ken Calman* (Sir Kenneth Calman, UK Chief Medical Officer) *concerning the Council's lack of support for the area, and also other issues surrounding the RCP review* (the 1996 Joint Royal College's Report CR54). ***Dr Davies and the Press Office have been kept informed of developments. I think that a carefully worded letter of reply from someone higher up in the Office might put this matter to rest**".*

It is hardly surprising that the ME/CFS community believes that there is no intention to address the psychosocial bias of the Wessely School and the damage that such bias causes to those who are physically sick, especially given that the MRC Portfolio in Mental Health Research stated "*Mental health in this instance covers…CFS/ME"* (Neurosciences Mental Health Board Strategy and Portfolio Overview Group Scoping Study, January 2005). When challenged, the MRC subsequently stated that CFS/ME was classified as a mental health problem for a "*pragmatic"* reason that was claimed to be *"related to the grants classification associated with the activities of one section of the office….The Mental Health Scoping Study included the PACE and FINE trials on the basis of the type of intervention being assessed, namely psychological interventions…".* The letter dated 6th December 2005 was from Dr Robert Buckle, who is now a member of the PACE Trial Steering Committee.

Members of MRC Boards are appointed to act *"as a core body of scientific advisors, assessing applications to the MRC".* The MRC's refusal to accept the international biomedical evidence about ME/CFS may be related to the fact that in 2002 / 2003 the following Wessely School members were appointed to MRC Boards: Professor Trudie Chalder; Professor Anthony Cleare; Professor Anthony David; Professor Anne Farmer, Professor Michael Sharpe, Professor Peter White; Professor Richard Bentall; Professor Philip Cowen; Professor Til Wykes and Dr SM Laurie, with Professors Simon Wessely and Francis Creed having been recent members (**http://www.mrc.ac.uk**). Wessely was a member of no less than three MRC Boards: the Health Services and Public Health Research Board; the Neurosciences and Mental Health Group and the Monitoring and Evaluating Group (MESG).

As Dr Jonathan Kerr, Sir Joseph Hotung Senior Lecturer in Inflammation, Department of Cellular and Molecular Medicine, Hon. Consultant in Microbiology, St George's University of London, stated at the Invest in ME Conference held in London in 2006:

"*It is rather sad that the MRC does not fund any biological studies such as we are doing, and I think the current…consideration of grant applications to the MRC on CFS is currently with the Neurosciences and Mental Health Board…and I think that (this) immediately biases the decision-making process because that panel is made up predominantly I believe of psychiatrists. It would be desirable if this could be reclassified* (by the MRC) *such that there would be money available…for biological approaches…It is a fact that currently the MRC does not fund any biological approaches".*

At the 2007 Invest in ME Conference, Dr Kerr repeated his message:

"*We have applied several times to the MRC and on each occasion we were invited to submit those applications and on each occasion we got scores typically of 9, 8 and 3 – the 3 score was obviously from a psychiatrist who was complaining about our way of enrolling the patients, the criteria we had etc…David Tyrell told me the MRC will never fund biomedical research in CFS because they are in the thrall of the psychiatrists – so far, he has been right".*

DVDs of both these Conferences are available from www.investinme.org

The late Dr David Tyrell, CBE, FRS, DSc, FRCP, FRCPath was Chairman of the UK National Task Force on CFS/PVFS/ME whose 1994 Westcare/DoH Report was rejected by the Wessely School and gave rise to their

own 1996 Joint Royal College's Report (CR54) that denied the existence of ME. In his Foreword to the 1994 Task Force Report, Tyrell wrote: "*We have no doubt that (ME/CFS) exist(s) and cause suffering and disability. We discuss the issue of nomenclature at some length for it is not just a semantic problem. It encompasses serious disagreements, which have sadly led to ill will and abusive remarks on such questions as whether the syndrome exists, whether it is 'real' or 'organic' or 'merely' psychological…it is important that…administrators, clinicians, scientists, funding agencies and patients identify the topics in their field on which action is needed…(and) the research community should be developed and strengthened. But we should be prepared for the long haul".*

It has certainly been *"a long haul"* because 15 years later, despite approximately 5,000 published mainstream papers that prove them wrong about the nature of ME/CFS, the Wessely School remains obdurate that "CFS/ME" is a somatisation disorder.

Lay Statements of concern about flawed studies

As part of the evidence that was obtained for the (unsuccessful) Judicial Review of the NICE Guideline in February 2009 at the High Court in London, statements from people with ME/CFS about their experiences of CBT and GET were obtained from 37 lay people.

Of concern is the evidence dated 22nd September 2008 of DC from Liverpool whose statement about Wessely School behavioural interventions confirmed:

"*I tried GET and from day one I followed the regime religiously. I would get weekly calls from my GET supervisor who I told exactly what I was experiencing. I never let up once with the incremental increases on the exercise bike and found that the project supervisor became more and more agitated when after three months I couldn't get any improvement from the programme. I pushed myself but found I did not recover. It just got harder and harder but I was told almost like a mantra that I must carry on, so I did. After three months—and I remember it well -- I pushed myself so hard to reach my target that other symptoms started to occur. I told the supervisor, who carried on the with 'GET rhetoric'…Finally I was referred to the CFS clinic…who informed my supervisor that I should stop…**I was informed that anyone who did not return for the post-GET assessment was to be considered 'recovered'. If this is the case then I feel whatever the results of the survey (they) would be skewed by correlation assessment not being carried out properly".***

This is an important statement because it confirms that anyone who did not return for post-GET assessment (because they may have suffered a serious relapse) was to be considered RECOVERED, which skews the statistics / data in favour of the alleged efficacy of what is in fact a failed intervention. If true, that is scientific fraud.

Another statement (from VJ, 13th October 2008) confirms: "*I am a fellow ME sufferer. I have had CBT at King's Hospital in London which neither helped nor made me worse. However, I did approach my GP and Consultant at the Chronic Fatigue Unit about getting the battery of tests recommended under the Canadian Guidelines and was fudged each time as to why they would not go through with these.* ***I was told I fitted the Oxford criteria and that would be enough when dealing with permanent health insurers and the DWP, and also that the Canadian Guidelines tests were not tests they saw any reason to do on ME sufferers".***

Definitions of Cognitive Behaviour Therapy and Graded Exercise Therapy as used in the PACE Trial

Simon Wessely has publicly stated: "***CBT is directive – it is not enough to be kind or supportive***" (New Statesman, 1st May 2008) and the form of CBT used in the PACE Trial is indeed "directive".

The Trial Identifier says: *"CBT will be based on the illness model of fear avoidance. There are three essential elements: (a) Assessment of illness beliefs and coping strategies, (b) structuring of daily rest, sleep and activity, with a graduated return to normal activity, (c) challenging of unhelpful beliefs about symptoms and activity"* and that it

says about GET: *"GET will be based on the illness model of both deconditioning and exercise avoidance. Therapy involves negotiation of an individually designed home aerobic exercise programme with set target heart rates and times"* (Section 3.2). The "Invitation to join the PACE trial" leaflet says: "*CBT is about examining how your thoughts, behaviour and CFS/ME symptoms relate to one another"* and says "*GET is about gradually increasing your physical activity to make you fitter and get your body used to exercise again".*

Referring to (ME)CFS and fibromyalgia as somatoform disorders, and citing an article by Wessely et al, a 2005 paper from Norway (Biological sensitisation and psychological amplification: Gateways to subjective health complaints and somatoform disorders. Ingvard Wilhelmsen. Psychoneuroendocrinology 2005:30:990-995) fuelled the "CFS/ME is a somatoform disorder" controversy:

"*What messages do we want to convey to the public? I will propose three slogans:*

1. *Do not listen to your body's signals! In other words, don't amplify.*
2. *Do not trust your feelings!*
3. *Do not trust your thoughts!*

"This is the central theme of CBT. It is an important message to the public that subjective health complaints are common and seldom an indicator of serious disease. Cognitive, emotional and behavioural factors have the capacity to relieve symptoms and even change the brain. These facts should be highlighted in our message to the public".

Such a message could prove fatal for some ME/CFS sufferers.

It runs directly counter to the advice given fifteen years earlier by Dr Darrel Ho-Yen about CBT/GET: *"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 (Wessely S, David A, Butler S, Chalder T: Management of chronic (postviral) fatigue syndrome. JRCGP 1989:39:26-29).* ***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****"* (JRCGP 1990:40:37-39).

"A CBT model of CFS/ME"

The Trial Manual for Participants who were allocated to the cognitive behavioural therapy (CBT) arm of the trial refers to a *"CBT model of understanding CFS/ME"* which in the next line has become a *"CBT model of CFS/ME".*

There is no "*CBT model of understanding*" in respect of understanding any disorder: people either understand something or they do not.

How offensive it would be if psychiatrists talked about a "CBT model of understanding" HIV/AIDS, or a "CBT model of understanding" breast cancer, or a "CBT model of understanding" multiple sclerosis, or diabetes (which seems to be already happening – see above)**.**

Medical knowledge does not rely on a "CBT model of understanding" a disease but relies on the science of medicine. To impose such a false doctrine upon patients with ME/CFS seems tantamount to psychological abuse of defenceless sick people.

Equally, there is no "*CBT model of CFS/ME*". The term appears to have originated with the Wessely School: "*A cognitive model of ME/CFS has been proposed (Sharpe et al 1991)"* (Interpretation of symptoms in chronic fatigue syndrome. Dendy C, Cooper M, Sharpe M. Behaviour Research and Therapy 2001:39(11):1369-1380). The Sharpe et al 1991 reference is to the Wessely School's own (Oxford) criteria (JRSM 1991:84:118-121).

Sharpe describes the *"cognitive model of CFS/ME"* as follows: "*A cognitive model of CFS, based on systematic observation of over 100 patients meeting criteria for CFS, has been proposed. The model as a whole attempts to explain how early life experiences lead to the formation of assumptions that, combined with certain life stressors, may precipitate CFS in predisposed individuals. The model then attempts to explain how cognitive, behavioural, biological and social factors interact, in a vicious circle, to perpetuate or maintain the illness.* ***According to this model, the interpretation of symptoms predominantly in terms of physical illness, and not in terms of negative emotional states, plays a particularly important role in the maintenance of the disorder".***

To base a theoretical model on around 100 patients, whilst subsequently ignoring the extensive biomedical evidence obtained on over 20,000 patients showing on-going viral activity and a disrupted immune system as perpetuating factors in ME/CFS, thereby wasting millions of pounds sterling trying to prove the validity of their non-existent "CFS/ME" model, is something for which many people believe the Wessely School ought to be held to account.

Between them, the international experts who compiled the 2003 Canadian criteria had examined over 20,000 patients and had extensive clinical, academic and research experience. **Known, on Wessely's own admission,** (R&D annual reports by NHS organisations in England for 2007: South London and Maudsley NHS Trust: Section 2A) **to have been advised by the Wessely School, the authors of the NICE 2007 Clinical Guideline 53 on "CFS/ME" recommended that UK clinicians should not use the Canadian Guidelines.**

For the PACE Trial Investigators to transform "*a cognitive model of CFS*" into a "*CBT model of CFS/ME"* seems to show how far from rigorous scientific standards those at the MRC with responsibility for vetting the PACE Trial have been prepared to depart.

Peter White tried to reinforce the concept of the "cognitive behavioural model of CFS" in his presentation to the Scientific Workshop sponsored by the US National Institutes of Health on 12th -13th June 2003 held in Bethesda, Maryland: *"Re: appropriate models,* ***Dr White explained that the cognitive behavioural model of CFS posits that the symptoms and disability of CFS are perpetuated predominantly by dysfunctional illness beliefs and avoidant coping. Beliefs associated with a poor outcome in CFS include that exercise is dangerous or damaging, that the cause of CFS is a virus, and that CFS is a physical illness****"* (summary by Daniel Clauw MD: http://web.archive.org/web/20080720081848/www.ahmf.org/medpolpace.htm).

The same meaningless term (*"the cognitive behavioural model of CFS/ME")* appeared in the draft Guideline on "CFS/ME" that was issued by NICE in September 2006 and which was savagely criticised by numerous Stakeholders. One such response was submitted by Dr Neil Abbot, Director of Operations for the charity ME Research UK (MERUK), whose submission was unambiguous.

Referring to the statement: *"A programme of CBT should include: ……explanation of the CBT model for CFS/ME"* (pages 17-24 of the draft Guideline), Abbot was explicit: ***"There is no CBT model for ME/CFS per se****. Rather there is CBT, a form of psychotherapy, which can be applied to all illnesses through the supposed biopsychosocial model.* ***Its application for people with ME/CFS would therefore be as a management tool, and not as an overarching model for the pathophysiology of illness".***

Both NICE and the MRC disregarded the extensive evidence supplied to both institutions demonstrating that the approach to ME/CFS of the MRC Principal Investigators increasingly seems scientifically invalid.

The result is the social phenomenon of mass delusion that seems to have been caused by the apparent contempt for patients and the apparent arrogance and elective ignorance of the PACE Trial's Principal Investigators who have persistently refused to heed the scientific evidence that their views about the nature of ME/CFS are scientifically insupportable.

The whole concept of "*a CBT model of CFS/ME*" is the fallacy of the Wessely School and consequently of the MRC, NICE, and the Department for Work and Pensions (which, as noted above, is jointly funding the PACE Trial and where psychiatrist Peter White is lead advisor on "CFS/ME").

The troubling issue of CBT/GET as the sole intervention for ME/CFS

The Wessely School do not claim that there is no physiological explanation for the symptomatology of "CFS/ME" -- it is described on pages 9-16 of the PACE Trial CBT Manual for Participants; their claim is that there is no pathology causing those symptoms. They do not seem to distinguish between physiology and pathophysiology but assert that the physiological changes result from deconditioning and are therefore reversible by CBT and GET. The folly of such a belief is easily demonstrated. For example, on page 11 of the CBT Manual for Participants is given the "physiological" explanation for visual problems and hyperacusis seen in ME/CFS: *"Visual and hearing changes: prolonged bed-rest results in a 'headward' shift of bodily fluids. This may result in visual problems and sensitivity to noise"*. This disregards the fact that ambulant people with ME/CFS also experience these problems. The quotations below from the Manuals (in Section 4) provide further examples of such misleading reasoning.

Moreover, the Wessely School themselves already know that the very modest benefit in only some patients who have undergone CBT has been shown by the Wessely School themselves to last for only 6 – 8 months and that *"the 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).

This was confirmed by others: in his Summary of the 6th AACFS International Conference in 2003, Charles Lapp, Associate Clinical Professor, Duke University, and Director, Hunter-Hopkins Centre, North Carolina, 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.

The Dutch Report showing that CBT does not work in ME/CFS

A Dutch report of February 2008 by Drs MP Koolhaas, H de Boorder and Professor Elke van Hoof (http://www.immunesupport.com/library/showarticle.cfm/ID/8724) comes to unambiguous conclusions about CBT for ME/CFS:

"In recent years, Chronic Fatigue Syndrome, also known as Myalgic Encephalomyelitis (ME/CFS), has been getting a lot of attention in scientific literature. There is as yet no consensus about the treatment of ME/CFS. The different treatments can be subdivided into two groups, the pharmacological and the psychosocial therapies.

"Most of the scientific articles on treatment emphasize the psychosocial approach. The most intensively studied psychological therapeutic intervention for ME/CFS is cognitive behaviour therapy (CBT). In recent years several publications on this subject have been published. These studies report that this intervention can lead to significant improvements in 30% to 70% of patients, though rarely include details of adverse effects.

"This pilot study was undertaken to find out whether patients' experiences with this therapy confirm the stated percentages. Furthermore, we examined whether this therapy does influence the employment rates, and could possibly increase the number of patients receiving educational training, engaged in sports, maintaining social contacts and doing household tasks.

"Method: By means of a questionnaire posted at various newsgroups on the Internet, the reported subjective experiences of 100 respondents who underwent this therapy were collected. These experiences were subsequently analysed.

"Results:

- *Only 2% of respondents reported that they considered themselves to be completely cured upon finishing the therapy*
- *30% reported 'an improvement' as a result of the therapy*
- *The same percentage [30%] reported no change*
- *38% said the therapy had affected them adversely, the majority of them even reporting substantial deterioration*
- *Participating in CBT proved to have little impact on the number of hours people were capable of maintaining social contacts or doing household tasks*
- *A striking outcome is that the number of those respondents who were in paid employment or who were studying while taking part in CBT was adversely affected. The negative outcome in paid employment was statistically significant.*

"A subgroup analysis showed that:

- *Those patients who were involved in legal proceedings in order to obtain disability benefit while participating in CBT did not score worse than those who were not*
- *Cases where a stated objective of the therapy was a complete cure did not have a better outcome*
- *Moreover, the length of the therapy did not affect the results.*

"Conclusions: This pilot study, based on subjective experiences of ME/CFS sufferers, does not confirm the high success rates regularly claimed by research into the effectiveness of CBT for ME/CFS.

"Overall, CBT for ME/CFS does not improve patients' well-being: More patients report deterioration of their condition rather than improvement.

"Our conclusion is that the claims in scientific publications about the effectiveness of this therapy, based on trials in strictly controlled settings within universities, have been overstated and are therefore misleading" (Source: Medisch Contact, February 2008, ISBN: 978-90-812658-1-2, by Koolhaas MP, de Boorder H, van Hoof E. The Netherlands. Information from m.p.koolhaas@consunet.nl).

A University of East Anglia conference has exploded the widespread myth that CBT is more effective than other types of therapy. CBT has been the subject of massive Government investment, as in the £8.5 million awarded for the setting up of "CFS" Centres specifically to deliver CBT to "CFS/ME" patients, and the millions of pounds sterling awarded to the Wessely School psychiatrists by the MRC to support the claimed efficacy of CBT in "CFS/ME" (said by Professor Sharpe in 2007 to have risen to about £4 million: Co-Cure ACT:RES:22nd Octber 2008), and recently CBT has been the subject of a £173 million Government grant.

The UEA conference was told: "***The Government, the public, and even many health officials have been sold a version of the scientific evidence that is not based in fact, but is instead based on error***". The conference was told that three combining factors have helped perpetuate the CBT myth: (i) more academic researchers subscribe to the CBT approach than to any other; (ii) these researchers get more research grants and publish more studies on the alleged effectiveness of CBT and (iii) this greater number of studies is used to imply that CBT is effective (News Desk, 18th July 2008).

International concern about the efficacy of CBT is to be found on the US CDC website: *"**The utility of CBT for CFS is in its formative stages and much needs to be learned before the limits of its usefulness are known**"* (http://www.cdc.gov/cfs/docs/wb3151/appendix-c.pdf). There is an abundance of evidence that CBT is unsuccessful, not only in "CFS/ME" but in wider applications, yet the MRC Data Monitoring and Ethics Committee and Trial Steering Committee apparently paid no heed to this evidence that was brought to the MRC's attention.

Could it be that, blinded by the brilliance of UNUMProvident's strategy to withhold or withdraw State and insurance benefits from claimants with ME/CFS (see below), the UK Government (and the Wessely School psychiatrists who act as its advisers on "CFS/ME"), the NHS, the Department of Health, the Department for Work and Pensions and the Medical Research Council all prefer their personal conviction to actual evidence?

Attempts to re-classify ME/CFS as a mental disorder

The intensity of Peter White's dissatisfaction with current classification of CFS, ME and PVFS (Post-viral fatigue syndrome) in ICD-10 was evident in his presentation to the Royal Society of Medicine's conference on "CFS" in April 2008 (Professor Peter White, Bart's and the London School of Medicine: What is Chronic Fatigue Syndrome and what is ME? Webcast: http://rsm.mediaondemand.net/player.aspx?EventID=1291 Power Point slides: http://www.roysocmed.ac.uk/chronicfatigue08/white.pdf).

White was unequivocal in advising clinicians not to use the ICD-10 classification of ME/CFS as a neurological disease; his words *(verbatim*) were:

"I'm going to try to define what Chronic Fatigue Syndrome is. By doing so, I'm going to review the ICD-10 criteria for the illness and see if they're helpful. The answer will be, they are not helpful…..This meeting is about clinicians making the diagnosis and helping patients…..Then we come the three clinical criteria to see if they're useful, and two of them actually do have help to us: the NICE Guidelines criteria and the Royal College of Paediatrics and Child Health criteria I would commend to you".

For the avoidance of doubt, the NICE Guideline CG53 recommends CBT/GET and very limited investigations, whilst the RCPCH Report of December 2004 (Evidence-based Guidelines for the Management of CFS/ME in Children and Young People) bears little relationship to children and young people with ME/CFS. The College's view of ME/CFS is that it is a behavioural disorder. The RCPCH report emphasised behavioural interventions: "*Children and young people with CFS/ME should be considered for graded exercise or activity programmes"* and contributors referred to the "*emotional dimensions of the illness"* and stated: *"The overarching aim of CBT is to help patients modify their behaviour for their own benefit".*

White then said that there was another important clinical point that he was going to make: "*that is – the diagnostic labels we choose to use influence our patients and influence prognosis…One of our problems is: labels do count".*

"Does the ICD-10 help us? Unfortunately not; there are at least five ways of classifying CFS using the ICD-10 criteria. What are they? We start off well: myalgic encephalomyelitis is in the neurology chapter of ICD-10… and helpfully, "chronic fatigue syndrome, postviral". So it starts off well. What if the viral illness is not a clear trigger for the illness? Well, you've got alternatives: in the Mental Health Chapter, you've got Neurasthenia…if you think that somehow, psychological factors have some role to play".

White then discussed the various somatoform classifications for chronic fatigue before saying: "*the trouble with these diagnoses is, you somehow have to guess that psychological factors have an important role to play in their aetiology".*

He concluded his presentation: *"It's confusing, isn't it?….ICD-10 is not helpful* ***and I would not suggest, as clinicians, you use ICD-10 criteria. They really need sorting out, and they will be in due course, God willing".***

That was a clear instruction to clinicians to disregard the ICD-10 classification of ME/CFS as a neurological disorder.

In an April 2009 paper, Peter White and co-authors concluded that their data *"suggest that fatigue syndromes are heterogeneous, and that CFS/ME and PVFS should be considered as separate conditions,* ***with CFS/ME having more in common with IBS (Irritable Bowel Syndrome) than PVFS does****. This requires revision of the ICD-10 taxonomy, which classifies PVFS with ME"* (Psychol Med 2009:Apr 15:1-9 PMID:19366500).

This seems another example of inconsistency on Peter White's part, because here he is saying that "CFS/ME" has more in common with irritable bowel syndrome, but this is the exact opposite of his comments to NICE about the draft Guideline, where he asserted: "***bowel symptoms are not part of CFS/ME"*** (St Bartholomew's Hospital Chronic Fatigue Services, Stakeholder comments on Chapter 6 of the draft Guideline on "CFS/ME", page 316). Such an assertion is all the more curious because the MRC website includes "*gastrointestinal problems"* in its description of "CFS/ME" and Peter White was involved with the 1994 UK Task Force Report on ME / CFS / PVFS which on page 71 at section 14.6.1 states: "*Given that symptoms of irritable bowel syndrome are common and that some patients develop food sensitivities, this is an area which urgently needs to be further studied*". It is therefore remarkable that in his Stakeholder submissions to the NICE draft Guideline twelve years later, Peter White still denied the existence of bowel problems in "CFS/ME", yet in order to support his call for a revised ICD taxonomy, he now claims that "CFS/ME" has more in common with irritable bowel syndrome than with PVFS.

Recent papers by Wessely and Hotopf have discussed fatigue and the evidence for the concept of neurasthenia – formally classified in ICD-10 Chapter V at F48.0. As noted above, sixteen years ago, Wessely asserted that neurasthenia *"would readily suffice for ME"* (Lancet 1993:342:1247-1248) and his belief remains firmly fixed despite the significant biomedical evidence that has emerged in the intervening sixteen years which proves his belief to be false.

Professor Michael Sharpe and his fellow psychiatrist Professor Francis Creed (leader of the European Medically Unexplained Symptoms [MUS] Study Group) are members of the DSM-V (Diagnostic and Statistical Manual-V that is due in May 2013) Somatic Distress Disorders Workgroup that is redefining the so-called "Somatoform Disorders".

Of relevance to the PACE Trial is the proposal of the Somatic Distress Disorders Work Group to create a category of "*Psychological factors affecting a medical condition*" that would allow a co-morbid diagnosis of *"somatic symptom disorder"*, thereby erasing the interface between psychiatry and medicine because this proposed new category would apply equally to a *"well recognized organic disease or a functional somatic syndrome such as irritable bowel syndrome or chronic fatigue syndrome"* (Editorial: J Psychosom Res. 2009: 66(6):473-6 http://www.jpsychores.com/article/S0022-3999(09)00088-9/fulltext).

As a (nominally) separate project, Professor Michael Sharpe is also the UK Co-Chair of the international CISSD (Conceptual Issues in Somatoform and Similar Disorders) Project, for which the charity Action for ME (to which Professor Sharpe is an *ad hoc* medical advisor) was the principal administrator. The only information that Action for ME has ever published on the project is to be found in their accounts and it is mystifying: it is referred to as the "*WHO Somatisation Project"* and it says: "*This grant is provided to help lobby the World Health Organisation for the recognition of M.E.* ***and its re-categorisation as a physical illness".*** Given that the WHO has classified ME as a physical illness for the last 40 years, this statement from Action for ME is inexplicable.

The CISSD project was the brainchild of Richard Sykes PhD (director of the former ME charity "Westcare" that has now been subsumed within Action for ME) who states that the impetus for it was the suggestion by many psychiatrists and others that "CFS" should be regarded and classified as a "mental" disorder that falls within the category of somatoform disorders and the difficulties this caused for patients. The project aimed to consider the whole spectrum of current somatoform classification; membership comprised over 80 advisors with a core work group of 33 members, the large majority being psychiatrists.

Sykes notes: "*It is true that CFS is listed under 'syndrome' in Volume III, the Index of ICD-10, and placed in G93.3, a category of neurological illness. But there remain problems: (1) some psychiatrists and others contest this classification of CFS as a neurological disorder and (2) 'fatigue syndrome' is listed in ICD-10 as F48, a mental disorder – which creates the apparent anomaly that 'fatigue syndrome' is a mental disorder, but 'chronic fatigue syndrome' is a neurological disorder"* (http://tinyurl.com/yz88mks).

One respected patients' advocate commented on Sykes' summary of his project:

"So basically, Richard Sykes created a "honey pot" for the discussion of CFS in relation to Somatoform Disorder and all the bees came to the honey pot. We only have his word that there is now a greater chance that CFS will be kept as a neurological classification. The people who came to the honey pot are still far more powerful than Sykes and what's more the combined force of those who came to the honey pot could just have had the effect of making their collective voice more powerful still.

*" I do not believe that **any** somatoform psychiatrists have **any** intention of letting go of CFS. Physical symptoms – blame the patient – no underlying disease processes found – ignore the available research and evidence. They demonstrate time and again that these "professionals" really only care for their shared beliefs more than they care for the facts or the truth or the patients. World wars have been fought to overcome powerful individuals who share this sort of behaviour"* (www.meactionuk.org.uk/commentonsykes.htm).

Many of those who have informed the CISSD Project are highly influential, internationally published researchers and clinicians in the field of psychiatry and psychosomatics and include Kurt Kroenke, Richard Mayou, Per Fink, Peter Henningsen, Veronque de Gucht, Bernd Löwe, Wolfgang Hiller and Winfried Rief. At least five members of Sykes' Project have gone on to become members of the American Psychiatric Association Work Groups, with four having been appointed to the DSM-V Somatic Symptoms Disorders Work Group (Professors Michael Sharpe, Francis Creed, Arthur Barsky and James Levenson), with Javier Escobar being appointed a member of the DSM-V Task Force.

Throughout their professional lifetime many of these psychiatrists have held entrenched views and have built their careers upon them; it is unrealistic to suppose that they will relinquish those views in the interests of mere medical science.

Barksy, for instance, is well-known for his belief that ME/CFS patients' suffering "*is exacerbated by a self-perpetuating, self-validating cycle in which common somatic symptoms are incorrectly attributed to serious abnormality, reinforcing the patient's belief that he or she has a serious disease. Four psychosocial factors propel this cycle of symptom amplification: the belief that one has a serious disease; the expectation that one's condition is likely to worsen; the 'sick role' including the effects of litigation and compensation; and the alarming portrayal of the condition as catastrophic and disabling"*. He then added another exacerbating factor: "*a clinical approach that over-emphasises the biomedical and ignores the psychosocial factors"*. He continued: "*symptom amplification operates in each individual sufferer. It may also serve as a mechanism for 'transmitting' the syndrome from one person to another"*. Barsky ended his article by calling upon the media, saying they must offer "*a less sensational, more accurate and more sophisticated model"* of functional somatic syndromes, in which he includes ME/CFS, fibromyalgia and irritable bowel syndrome (Ann Intern Med 1999:130:11:910-921).

Letters sent to the journal commentating on the Barsky paper included the following:

"*the authors were allowed to present opinions as facts and to ignore the many studies that undermined their hypothesis. Their lack of objectivity resulted in the publication of a poorly-researched article which misrepresented the research and perpetuated myths. What happened to evidence-based medicine?"* (EM Goudsmit PhD)

"Barsky and Borus managed to omit several hundred of peer-reviewed articles documenting physiologic bases for illnesses such as the chronic fatigue syndrome. Even the review of the psychological literature left out articles inconsistent with Barsky and Borus' speculations and sometime inaccurately portrayed the research they included" (TE Hedrick PhD)

"I've never been able to determine how secondary gains that include financial hardship, social isolation and reduced quality of life can perpetuate illness behaviour" (J McSherry MB ChB)

"***The authors claim that (CFS) has 'enough in common' with other syndromes for them to be lumped together. Since when was 'enough' a suitable quantification to pass peer review?"*** (K Clemenger BS)

"*A shocking article appeared in a widely read medical journal that seemed to turn back history. The authors argued that all somatic illnesses, those without a clear explanation of the cause, are fake. Such diseases, these psychiatrists argued, are little more than the expression of unhappy people who are desperate for attention. The authors further stated that doctors who appear to be 'sympathetic' to such patients only encourage these bogus maladies to persist"* (Faces of CFS: Case Histories of Chronic Fatigue Syndrome. David S Bell. Lyndonville Publications, New York, 2000).

Given the well-known and resolute commitment of the PACE Trial Principal Investigators (Professors Sharpe, White and Chalder) – and their powerful paymasters the medical and permanent health insurance industry -- to recategorising "CFS/ME" as a mental disorder, and given the Wessely School's success in ensuring that the NICE Guideline rejected the ICD-10 neurological classification that has held good for the last 40 years, and given the PACE Trial team's forecast that the outcome of the Trial will inform any future revision of the NICE Guideline on "CFS/ME", particularly given the content of the PACE Trial Manuals, it would be foolhardy to hope that the CISSD report will be able to counter such a determined strategy by such powerful and influential advocates.

The CISSD project includes psychiatrists who do not believe patients and who seem to denigrate them, and who also ignore voluminous research evidence, so the long-running battle of the Wessely School's unproven beliefs versus biomedical science seems set to continue.

For additional information about the CISSD Project and on the progress of the DSM and ICD revision processes, see http://meagenda.wordpress.com/dsm-v-directory/ (to whom grateful acknowledgment is made).

Attempts to reclassify irritable bowel syndrome (IBS) as a mental disorder

Peter White's call for the separation of PVFS from "CFS/ME" and for a consequent revision of the ICD taxonomy seems a clear indication of his intention to reclassify "CFS/ME" as a somatoform disorder, along with irritable bowel syndrome (IBS), which the Wessely School believe is also a somatoform disorder (Lancet 1999:354:936-939) in defiance of the evidence that it is not, of which the following are recent illustrations:

- at the 68th Annual Scientific Meeting of the American College of Gastroenterology held in 2003 at Baltimore, important findings were presented by lead investigators from the University of Vermont (Peter Moses, Associated Professor of Medicine and Director of Clinical Research in the Digestive Diseases, and Gary Mawe, Professor of Anatomy and Neurobiology): "*Serotonin is a critical signalling molecule necessary for normal gut function. Our finding that key elements of serotonin signalling*

are changed in IBS lends credibility to the notion that IBS is not simply a psychological or social disorder as was once thought, but instead due to altered gut biochemistry and interactions between the gut and the brain. Now we have a perspective on molecular changes in the intestines of individuals with IBS that we did not have before. We identified a significant decrease in the serotonin transporter in cells that form the inner lining of the bowel. Because the transporter is diminished in IBS, serotonin stays around longer, and this can lead to changes in motility, secretion, and sensitivity" (Ecotoxicology 2003:12 (1-4):345-363)

- in 2006, the BMJ Learning Programme by a Clinical Research Fellow and a Professor of Medicine and Gastroenterology featured IBS (BMJ 2006:332:280-283). This programme pointed out that a number of pathophysiological abnormalities can often be identified: "*IBS is now clearly understood to be a multifactorial condition, rather than its just being due to psychopathology. These include motility, visceral sensation, central processing, genetics, inflammation and neurotransmitters"*

- at the American Academy of Neurology 59th Annual General Meeting held in Boston in April / May 2007, researchers from Brazil showed that people with inflammatory bowel disease are at risk of developing subsequent neurological disorders and presented convincing evidence of the link between inflammatory bowel disease and peripheral neuropathy: "*Based on these results, we believe IBD itself is directly related to the neuropathy and that neuropathy in these patients is much more common than previously thought"*

- regarding IBS in ME/CFS specifically, there is evidence that the disorder is accompanied by an increased translocation of endotoxins of gram-negative enterobacteria through the gut wall, with signs of activation of the inflammatory response system and IgG3 subclass deficiency (Maes M et al. Neuro Endocrinol Lett 2007:28:6).

Clearly, the out-dated hypothesis that IBS is a psychosomatic disorder has been abandoned by those clinicians who fulfil their contractual obligations to keep up-to-date with medical science, yet the Wessely School seem intent on ignoring this progress in medical knowledge.

Moreover, the PACE Participants' Newsletter Issue 3 (December 2008) was disparaging about the published work of Dr John Chia from California, who has compellingly demonstrated the presence of enterovirus in the stomach of people with ME/CFS. Enterovirus infections have previously been reported in UK studies of ME/CFS patients. Enteroviruses are a genus of RNA viruses that includes echovirus, coxsackie virus and poliovirus. In a study by John Chia, of 108 patients with ME/CFS who underwent gastric biopsies, 100 revealed chronic inflammation and 80% were positive for VP1 (Viral Protein 1). Enteroviral RNA was detected in 33% of patients.

VP1 or enteroviral capsid protein was first used by Professor James Mowbray et al in the UK in 1988 but dismissed by Wessely as *"unsuitable for routine clinical use"* [Lancet 1989:1:1028-9] and the test is no longer available in the UK.

The PACE Newsletter Issue 3 says about Dr Chia's internationally acclaimed work: "*The laboratory work looked convincing, but many patients had significant gastro-intestinal symptoms and even signs, casting some doubt on the diagnoses of CFS being the correct diagnosis in these patients"* (http://listserv.nodak.edu/cgi-bin/wa.exe?A2=ind0906a&L=co-cure&T=0&O=D&P=3433). To dismiss such findings in an apparent attempt to influence PACE Trial participants, whilst the same issue contained fulsome praise for CBT, might be deemed unethical.

Attempts to reclassify fibromyalgia (FM) as a mental disorder

Fibromyalgia is another disorder that the Wessely School believe to be a somatisation disorder (Lancet 1999:354:936-939) -- indeed, Wessely et al state that there is only one "*functional somatic syndrome*".

To the consternation of medical scientists and contrary to accepted scientific practice, the Wessely School decided to include fibromyalgia patients in the MRC PACE Trial, which means that the PACE Trial includes at least three distinct disorders -- ME/CFS (ICD-10 G93.3); fibromyalgia (ICD-10 M79.0) and psychiatric fatigue (ICD-10 F48.0).

At the International Science Festival held on 9th April 2004 in Edinburgh, Michael Sharpe spoke in a debate entitled "Science and ME" and was specifically asked if patients with fibromyalgia (FM) were to be included in the PACE Trial of "CFS/ME". Sharpe replied in the affirmative, implying that patients with FM needed to be included in order to reach the recruitment target. He said *(verbatim)*: *"We **want** broadness and heterogeneity in the trial".*

On 15th April 2005 the MRC confirmed by letter to a correspondent (Neil Brown): *"When researchers put together a proposal they are required to define the population they are studying"*. Why this basic requirement is not applicable to the PACE Trial and quite how the outright abandonment of this principle might affect the statistical analysis of the PACE Trial has not yet been clarified.

That FM patients were to be included in the PACE Trial was further confirmed on 12th May 2004 by Parliamentary Under Secretary of State at the Department of Health, Dr Stephen Ladyman, at an All Party Parliamentary Group on Fibromyalgia, who announced that doctors were being offered financial inducements to persuade patients with FM to attend a "CFS" Clinic to aid recruitment to the PACE Trial (EIF: Spring/Summer 2004, page 19).

This caused written representations to be made to the MRC, because FM is classified as a distinct entity in ICD-10 at section M79.0 under Soft Tissue Disorders and it is not permitted for the same condition to be classified to more than one rubric, so concern was expressed as to how the intentional inclusion of disparate disorders could yield meaningful results, especially as FM was expressly excluded from the Systematic Review of the literature on CBT/GET carried out by the Centre for Reviews and Dissemination at York, whose authors were categoric: *"Studies including patients with fibromyalgia were not selected for review"* (JAMA 2001:286:11:1360-1368). The literature is quite clear that those with both FM and ME/CFS have worse physical functioning than those who have ME/CFS alone, and that *"fibromyalgia appears to represent an additional burden of suffering amongst those with (ME)CFS"* (Rheum Dis Clin N Am 1996:22:2:219-243). Jason et al also pointed out that FM and Multiple Chemical Sensitivity (MCS) *"represent additional illnesses of interest where issues of diagnostic accuracy are concerned"* (JCFS 1999:5:3-33).

FM has a distinct biological profile that is different from ME/CFS, so it is unclear how the intentional inclusion of different disorders in an MRC trial evaded detection by the allegedly rigorous monitoring process. **The MRC was asked how the deliberate inclusion of different disorders could not result in skewed and meaningless conclusions when, from the outset, patients being entered into the PACE trial were not clearly defined, a question that elicited no response.**

Apparently neither the MRC nor the West Midlands MREC is concerned with diagnostic accuracy.

Peter White states about fibromyalgia (Psychol Med 2009:15 April: 1-9:PMID: 19366500): *"the increased incidence of the diagnosis may more reflect a change in the fashion for the diagnosis of fibromyalgia by GPs"*, a common charge made by the Wessely School in relation to "CFS/ME", for example, Wessely himself decreed: *"It is regrettable that ME has become a disease of fashion, even a 'fad' "* (Recent Advances in Clinical Neurology, Churchill Livingstone 1990, pp 85-131).

White also asserts: *"**There is little doubt that patients with fibromyalgia have close comorbidities with several disorders that are regarded by many as functional disorders. These include: irritable bowel syndrome (and) CFS/ME. I have argued against this idea, suggesting that the commonality is abnormal illness behaviour, as seen in the process of somatisation**"* and he concludes: *"The final area of commonality between fibromyalgia and CFS concerns the social risk markers for maintenance of both disorders"*

(http://www.entretiens-du-carla.com/publication.php?pub=fibro&pg=fatigue).

This out-dated perception has been shown to be invalid, for example:

- *"Recent reports suggest that a subgroup of FMS subjects has an immune-mediated disease. EDX (electrodiagnostics) demonstrated a distal demyelinating polyneuropathy, suggestive of chronic inflammatory demyelinating polyneuropathy (CIPD)"* (Rheumatology 2008:47:208-211)

- a report in Neuroscientist, February 12th 2008 said: "*Neurotransmitter studies show that fibromyalgia patients have abnormalities in dopaminergic, opioidergic, and serotoninergic systems (and) studies of brain anatomy show structural differences between the brains of fibromyalgia patients and healthy individuals. The cerebral alterations offer a compelling explanation for the multiple symptoms of fibromyalgia"*

- electron microscopy studies of skin biopsies from FM patients have shown unusual patterns of unmyelinated nerve fibres as well as associated Schwann cells (Clin Rheumatol 2008:27(3):407-411)

- high plasma levels of MCP-1 and eotaxin provide evidence for an immunological basis of fibromyalgia, ie. fibromyalgia is associated with inflammatory chemokines (Exp Biol Med 2008 5th June)

- altered intestinal permeability has been demonstrated in fibromyalgia patients (Rheumatology 2008:47(8):1223-1227)

- changes in the levels of the neurotransmitter dopamine may explain brain gray matter reductions experienced by people with fibromyalgia. A study by Wood et al from Louisiana State University found significant reductions in gray matter in FM patients, confirming previous findings. The study also found that FM patients showed a stronger correlation of dopamine metabolism levels and gray matter density in areas of the brain where dopamine is known to control neurological activity (American Pain Society news release, June 16, 2009)

- a blinded, controlled study of neurological signs and symptoms in FM by researchers from the University of Washington, Seattle, demonstrated significant neurological findings on physical examination, with FM patients having more neurological symptoms -- in multiple categories – than controls. FM patients had greater dysfunction in cranial nerves IX and X (42% versus 8%), and more sensory abnormalities (65% versus 25%); more motor abnormalities (33% versus 3%), and more abnormal gait abnormalities (28% versus 7 %). The FM group also had significantly more neurological symptoms, with the greatest differences being photophobia (70% versus 6%), poor balance (58% versus 2%), and tingling in the arms or legs (54% versus 4%). Poor balance, tingling in limbs, and numbness in any part of the body correlated with neurological examination findings in the FM group (Watson NF, Buchwald D et al. Arthritis Rheum 2009:60(9):2839-2844)

- Ablin, Buskila and Clauw from the University of Michigan reviewed several objective biomarkers in fibromyalgia, commenting: "*Although there was original scepticism that any objective abnormalities would be identified in these individuals, at present there are many that have been reproducibly identified, and most point to dysregulation of central nervous system function as a key underlying pathogenic mechanism in this and related illnesses"* (Curr Pain Headache Rep 2009:13(5):343-349).

It is troubling that the Wessely School so persistently dismiss or ignore the evidence that fibromyalgia is not a somatisation disorder and that they disregard the evidence that FM and ME/CFS have distinct biological profiles, for example:

- levels of somatomedin C are lower in FM patients but are higher in ME/CFS patients (J psychiat Res 1997:31:1:91-96)

- levels of Substance P are elevated in patients with ME/CFS but not in patients with FM (Pain 1998:78:2:153-155)

- patients with FM are not acetylcholine sensitive (Rheumatology 2001:40:1097-1101) but patients with ME/CFS are acetylcholine sensitive (Prostaglandins, Leukotrienes and Essential Fatty Acids 2004:70:403-407)

- endothelin-1 is raised in fibromyalgia (Rheumatology 2003:42:493-494) but is normal in ME/CFS (Rheumatology 2004:43:252-253).

As others have asked: whatever happened to evidence-based medicine?

UNUMProvident Policy that underlies the MRC PACE Trial

It seems beyond doubt that Government policy is to target specific disorders for the primary purpose of reducing the number of claims for sickness and disability payments and that this is being effected with the assistance of the insurance company UNUMProvident (see Appendix III).

After the commercial interests of the disability insurance industry and its Wessely School "medical" advisors became influential in the UK benefits system, the situation for those with ME/CFS took a serious turn for the worse.

Dr Peter Dewis from the DWP Disability Living Advisory Board (who, together with Professor Mansel Aylward authored the Disability Handbook before Dewis became Chief Medical Officer at UNUMProvident) confirmed that before Attendance Allowance became the Disability Living Allowance (DLA), decisions on eligibility for State sickness and disability benefits were made by doctors (hence the "Handbook for Delegated Medical Practitioners"), but since the advent of DLA, such decisions are now made by non-medical personnel, and the "Disability Handbook" is a guide for these non-medical decision-makers.

During his time at the DWP, Aylward was well-known for his support for the Wessely School and for his opposition to disability benefits being paid to ME/CFS claimants. During his tenure at the DWP, Aylward is on published record as indicating his own and his Department's disapproval of the UK Chief Medical Officer's 2002 Report on "CFS/ME" (the Chief Medical Officer, Professor Sir Liam Donaldson, is on record on 11th January 2002 as stating that "CFS/ME" should be classified alongside multiple sclerosis and motor neurone disease) and of preferring the opinion of the psychiatrists who resigned from the Working Group because they did not get their own way in achieving the re-categorisation of "CFS/ME" as a somatic syndrome as they intended. Mansel Aylward's long association with UNUMProvident is a matter of record (see Appendices III and IV).

The Woodstock Connection

On 6th – 8th November 2001, key Wessely School activists attended the "Malingering and Illness Deception" Meeting in Woodstock, near Oxford. Those attendees were Professors Wessely, White, Sharpe and Aylward. All are involved with the MRC PACE Trial

Other attendees included staunch Wessely School psychiatrists Professors Christopher Bass and Anthony David and – importantly – Dr John LoCascio, representing UNUMProvident.

As Jonathan Rutherford, now Professor of Cultural Studies at Middlesex University, states in "New Labour and the end of welfare": ***"In the UK, two Woodstock participants, Professor Simon Wessely and Professor Michael Sharpe, were working on reclassifying ME/CFS as a psychiatric disorder. A change in classification would trigger the twenty-four month pay out limit on psychological claims and would save the industry millions of dollars".***

Because the matter is so important for those with ME/CFS, renewed attention is drawn to Rutherford's article published on 25th April 2007, from which the following quotations are taken:

"In November 2001 a conference assembled at Woodstock, near Oxford. Its subject was 'Malingering and Illness Deception'. Amongst the 39 academics and experts was Malcolm Wicks, Parliamentary Under Secretary of State for Work, and Mansel Aylward, his Chief Medical Officer at the Department of Work and Pensions (DWP). What linked many of the participants together, including Aylward, was their association with the giant US income protection company UnumProvident.

"New Labour was looking to transform the welfare system.

"UnumProvident introduced an aggressive system of 'claims management'.

"Specific illnesses were targeted in order to discredit the legitimacy of claims.

"In July 2004 (UnumProvident) opened its £1.6 million UnumProvident Centre for Psychosocial and Disability Research at Cardiff University. The company appointed Mansel Aylward as Director following his retirement from the DWP.

" Professor Peter Halligan, who had forged the partnership with UnumProvident, was ambitious: 'Within the next five years, the work will hopefully facilitate a significant re-orientation in current medical practice in the UK'.

"The two men were joined by Gordon Waddell, another Woodstock participant. In 2005 the centre produced 'The Scientific and Conceptual Basis of Incapacity Benefits' (TSO, 2005) written by Waddell and Aylward and published by the DWP".

(UNUMProvident hosted the launch of this book on 3st January 2006 at the Savoy Hotel, London; commenting on the book launch, Dr Peter Dewis, formerly Chief Medical Officer at UNUMProvident but at the time UNUMProvident's Customer Care Director, said: ***"We are delighted to be involved with the launch of this book as rehabilitation is an issue that is core to UNUMProvident's business proposition"*** (http://www.unumprovident.co.uk/Home/Corporate_Information/Press_Releases/2006/Book_Launch.htm).

Rutherford's article continued: *"The methodology used by Waddell and Aylward is the same one that informs the work of UnumProvident.*

*"In a memorandum submitted to the House of Commons Select Committee on Work and Pensions, UnumProvident define their method of working: '**Our extended experience has shown us that the correct model to apply when helping people return to work is a bio-psychosocial one'.***

*"Waddell and Aylward adopt the same argument. Disease is the only objective, medically diagnosable pathology. Sickness is a temporary phenomenon. **Illness is a behaviour**.*

"(Incapacity benefit) trends are a social cultural phenomenon, rather than a health problem.

"The solution is not to cure the sick, but a 'fundamental transformation in the way society deals with sickness and disabilities' (page 123).

"The goal and outcome of treatment is work.

"No-one who is ill should have a straightforward right to Incapacity Benefit.

"(In the US in 2004) Commissioner John Garamendi described UnumProvident as 'an outlaw company. It is a company that for years has operated in an illegal fashion'.

"UNUMProvident continues to exert its influence, aided by the ideological work of the Woodstock group of academics".

(http://web.archive.org/web/20080412085745/http://www.compassonline.org.uk/article.asp?n=563).

Symptoms or sickness?

In 2002 a book entitled "Work and Mental Health: An Employers' Guide" was published by the Royal College of Psychiatrists Publications. It was edited by Doreen Miller, Maurice Lipsedge (Emeritus Consultant Psychiatrist to the South London and Maudsley NHS Trust at Guy's Hospital who, like Michael Sharpe, works for UNUMProvident) and Paul Litchfield.

It was sponsored by the insurance company Swiss Life (UK) plc (for which Professor Peter White is Chief Medical Officer) which states about itself: "*Swiss Life (UK) plc provide life, critical illness and income protection products to employees and individuals, offering financial security during times of need. We are one of the UK's largest employee benefits protection providers, covering more than 1.6 million employees and their families, in approximately 8000 group schemes".*

In his contributed chapter to the book, PACE Trial Principal Investigator Michael Sharpe, together with Derek White, stated about "CFS/ME":

"Chronic fatigue syndrome (CFS), post-viral fatigue syndrome (PVFS), neurasthenia and myalgic encephalomyelitis (ME) are terms used to describe an idiopathic syndrome of chronic fatigue *and disability.*

"Patients may emphasise physical rather than emotional symptoms because of social stigma. Misleading information may reinforce this ' medical' bias.

"Prognosis is worse for patients who have a conviction that the cause is purely 'physical'.

"Assessment…should include the individual's beliefs about the illness.

"CBT places particular emphasis on helping patients to reappraise their illness beliefs.

"Work rehabilitation…can be a lengthy process and the success rate is moderate at best. Lack of, or refusal to accept, appropriate treatment by the National Health Service and misleading advice are common problems.

"The occupational physician may be asked to advise on retirement on grounds of ill-health, for which a common criterion is permanent inability to undertake normal duties – a requirement unlikely to be satisfied".

The Preface by John Cox (President of the Royal College of Psychiatrists) and Jim Sykes (President, Faculty of Occupational Medicine) states:

"*The hard work that each author and the editors have put into this book demonstrates a fundamental tenet of medical practice – doctors and other healthcare professionals working together in the best interests of their patients".*

There are many who would profoundly disagree that the Wessely School work together in the best interests of their patients.

Following another Woodstock conference in 2003, a book entitled "Malingering and Illness Deception" was published by Oxford University Press that year. It was edited by Peter Halligan, Christopher Bass and David Oakley. Simon Wessely contributed chapter 2 and Michael Sharpe contributed chapter 12.

It received rave reviews. One review (J R Coll Physicians Edinb 2005:35:126-127) containing the words "*imposters"* and *"invention"* by former Postgraduate Dean and Professor of Clinical Medicine RA Wood is glowing: "*GPs and hospital doctors recognise that patients tend to downplay their symptoms and cope remarkably well with disability, adjusting in a determined way and being positive.*

"There are also those, for example with ME, where the objective disablement is often less than the subjective assessment of the situation. But, in general, our interactions with patients are with people who are honest about their complaints and who are anxious to resume normal working, domestic and leisure activities as soon as possible.

"It is timely that there should now be a truly readable book which looks at the way in which patients misrepresent their illnesses. This 370 page paperback is a compilation of fully referenced papers given by a miscellany of most eminent contributors.

"Doctors in so-called advanced countries with benefits systems have simply got to get used to the truths and fictions that are discussed in this very important book. ***This book should be read by medical students (and) it is compulsory reading for any doctor writing a report for a legal purpose or providing certification of benefits****. The good news is that the conference from which it came was sponsored by the Department of Work and Pensions.*

"A decent sized chunk of our GNP (gross national product) is being sidelined into unjustifiable benefits, premature retirements (and) insurance costs.

"We as doctors are best placed to derail this gravy train.

"Several Benefits Agencies are no longer reluctant to obtain video evidence of the capacities of claimants.

"Doctors who have read this valuable book will help patients who will otherwise come to sacrifice their useful lives to imaginary disability".

Whilst no right-minded person objects to stringent measures being employed to identify benefit fraud, to include ME/CFS as one of the targeted "illness deceptions" and to describe it as "*an imaginary disability*" is preposterous.

Rutherford's quotations mentioned above come from the book by Professors Gordon Waddell and Mansel Aylward (The Scientific and Conceptual Basis of Incapacity Benefits, TSO, 2005, published following the Woodstock Conference that was funded by the DWP).

Parts of the 2005 book seem to have been cut and pasted from a book published the previous year by Professors Gordon Waddell and Kim Burton ("Concepts of Rehabilitation for the Management of Common Health Problems", TSO, 2004). This book was commissioned by the Corporate Medical Group of the UK DWP and acknowledges the work of prominent Wessely School members, including Mansel Aylward, Derick Wade, Peter White and Simon Wessely himself.

In the 2004 book, CFS is referred to by Waddell and Burton as a *"common* ***mental health*** *problem".*

Of concern is the fact that this book is listed by NICE as one of its references in its 2007 Clinical Guideline on "CFS/ME", because not only do Waddell and Burton discuss *"biological obstacles"* in relation to rehabilitation, they also assert: "*Symptoms are by definition subjective and therefore at least partly a matter of perception".*

"CFS/ME" is thus decreed to be a "perceptual problem", but this argument is not based on either logic or medical science.

Notwithstanding, in their 2005 book Waddell and Aylward are unambiguous, indeed asserting: "***The solution is not to cure the sick"*** but to get the sick removed from benefits, since *"no-one who is ill should have a straightforward right to Incapacity Benefit".*

This book sets out to separate "symptoms" from "disability". Whilst disease is acknowledged to be "*objective, medically diagnosed pathology"*, "symptoms" and "sickness" are not to be accepted as incapacity to work, and "illness" is to be reversed by cognitive restructuring of the person's aberrant beliefs that they are sick.

The authors assert that: "*symptoms are bothersome bodily or mental sensations"*; illness is merely: *"the subjective feeling of being unwell"* and: *"sickness is a social status granted to the ill person by society……Sickness and disability do not necessarily mean incapacity for work".*

Importantly, the intended eradication of ME/CFS seems to have been facilitated by both NICE and the MRC PACE Trial, both of which state that they have called the disorder "CFS/ME" in order to include both symptoms and disability, thus providing a route for those with "symptoms" to be "rehabilitated" by means of CBT and GET and then removed from benefits.

One of the PACE Trial's Principal Investigators, Woodstock attendee Michael Sharpe, had paved the way for this in his 2002 article "The report of the Chief Medical Officer's CFS/ME Working Group: what does it say and will it help?" (Clinical Medicine 2002:2:5:427-429):

"*CFS, sometimes known as ME, has long been a controversial topic.*

"Patients' organisations have been notably effective in lobbying parliament. Largely as a result of this political pressure…the then UK Chief Medical Officer took the unusual step of commissioning a special working group to report to him on the most effective methods of treatment and management for this condition.

"Five professional members resigned because they felt the recommendations had departed from the evidence base and were biased towards a biomedical rather than biopsychosocial perspective.

"The working party report uses both CFS and ME but declines to recommend one term over the other, preferring the compromise "CFS/ME".

"For many ME implies not only a 'real illness' but also a fixed and permanent disease like multiple sclerosis. This is a matter of concern to those who regard the condition as potentially reversible with appropriate treatment.

"An associated issue is whether CFS/ME is best regarded as a 'medical' or as a 'psychiatric' illness.

"In practice, the choice of treatment depends on whether the condition is assumed to be 'permanent' to be adjusted to by pacing, or seen as potentially reversible and to be actively treated with rehabilitation.

"Important controversies about the nature and management of CFS have been largely side-stepped in the report and its conclusions often read as an uneasy compromise. The adoption of the name CFS/ME symbolizes this".

The term "CFS/ME" was carefully constructed by the Wessely School because in their psychosocial model of disease, "symptoms" have nothing to do with disability, a concept that to most straight-thinking people is illogical but which fits into the Wessely School's rationale for GET: *"The objective is to improve the person's CFS/ME symptoms and functioning, aiming towards recovery"* (NICE CG53 Full Guideline, page 12).

The whole concept of "biopsychosocial" intervention would seem to be a short sighted 'quick-fix' that is doomed to pass into oblivion once the biomedical evidence falls into place: to disregard the need for (and the importance of) the bio*medical* aspects that are already known to underlie ME/CFS and to place such undue emphasis and funding only on the bio*psychosocial* aspects has, through the auspices of UNUMProvident and members of Peter White's One-Health company, come to dominate UK Government policy and service provision, but it may soon turn out to be the company's own death sentence because there is now so much credible biomedical evidence of serious organic pathology in ME/CFS that the beliefs of members of the One-Health company and the Wessely School look increasingly scientifically naïve and ill-founded.

For more evidence of the deliberate creation via social constructionism of "psychosocial" illness by the Wessely School's indoctrination of State agencies, and the impact of this on social and welfare policy, see "Proof Positive?" by Marshall & Williams (http://www.meactionuk.org.uk/Proof_Positive.htm).

There is substantial evidence that the State via its Wessely School advisors seeks to control both the medical profession and the sick themselves, and that the PACE Trial may be one of the tools by which such control is to be exerted.

The 2005 book by Gordon Waddell and Mansel Aylward that arose from the Woodstock Group meeting acknowledges the input of key Wessely School activists (Wessely, White, Sharpe and Wade, amongst others) and it provides insight into the hidden agenda of the PACE Trial.

It is clear that Waddell and Aylward (backed by UNUMProvident and the DWP) are seeking to change medical practice, including the behaviour of GPs.

Of particular concern is the fact that Waddell and Aylward (on behalf of the insurance industry and the State) want total control to decide who is sick and who is not, and they intend to restrict and control input from General Practitioners about which patients GPs may allow to be "sick", even discussing what threats should be made to those GPs who do not conform. Such threats include reporting non-compliant GPs to the General Medical Council (GMC) on a disciplinary charge.

At the All Party Parliamentary Group on ME (APPGME) meeting held on 21st October 2009 in Committee Room 21 at the House of Commons, the current Secretary of State for Health (the Rt Hon Yvette Cooper MP) was made aware of common problems faced by people with ME/CFS in relation to the DWP, **specifically the way in which a patient's own GP and specialist were progressively being removed from the opinion-gathering process and replaced by doctors who know nothing of the patient's social and medical background. In response, she noted these concerns but did not indicate that there would be any shift in the DWP position** (ME Association summary of APPGME meeting: http://tinyurl.com/ycnw6q5).

This is despite the concerns expressed on 29th April 2009 by their Lordships during the Second Reading of the Welfare Reform Bill (Hansard: Lords: vol. 710: no. 67: 301-302), including the Countess of Mar, who spoke about people with ME/CFS:

"*I cannot see the benefit of expending vast amounts of money and time on pretending to make a small group of vulnerable people supposedly fit for work…These people suffer from symptoms of fluctuating frequency and severity. Gulf War illness, fibromyalgia and irritable bowel syndrome are some of the others. (ME/CFS) has been defined as a neurological disease by the World Health Organisation and the level of disability it causes has been compared with congestive heart failure, multiple sclerosis, rheumatoid arthritis and other chronic conditions…**Despite the growing***

body of evidence that these diseases are biomedical, there is still a school of thought that they are psychosocial behavioural conditions and that they can be overcome with firm handling, a course of cognitive behaviour therapy and graded exercises. It is apparent that this view still prevails at the DWP. This is so despite Ministers' repeated assurances that they and the Department for Work and Pensions' employees and agents fully agree with the Department of Health statement that they 'accept the World Health classification of CFS/ME as a neurological condition'….*This Bill compounds the problems that have emerged from last year's welfare reforms.* ***The language is harsh, the sanctions punitive and the rule inflexible****. It appears that decision-makers will use subjective rather than objective measures as a basis for their plans…Past experience has shown that, no matter what the claimant tells the decision-maker or what his medical notes indicate, a claimant with a fluctuating condition is likely to be 'directed to undertake specific work-related activity in certain circumstances'. The Minister spoke about eliminating discrimination. To quote again from that report: 'The fact that people with ME cannot readily convey the reality of their illness experience on existing assessment forms or in early assessment interviews shows that, from the first interaction, such illnesses are discriminated against'….I am worried that there is no indication in the Bill of the level of training that will be required of the advisers and decision-makers or, if they are to be supplied by contract with the private sector, what practical and ethical checks will be made on their decisions".*

This DWP control (where Professor Peter White is lead advisor on "CFS/ME") seems to bear an alarming similarity to the National Socialist influence that swept across the Continent of Europe during the early 20th century.

In 2001, the American Journal of Bioethics published an article by Warren T Reich from Georgetown University who reported on an inquiry into ideas that were used to justify the shift of medical ethos in Germany prior to and during the Nazi era (AJOB 2001:1:1:64-74). Reich, Professor Emeritus of Bioethics in the Georgetown University School of Medicine, considers the evidence in relation to the current ethos of care of the sick and the manipulation of that care:

"*To develop an adequate ethic for the healthcare professions, we need to look more deeply into the sentiments and commitments of healthcare professionals…****If we pursue this, we encounter precisely the sort of ethic on which much of Nazi medicine was radically built, namely, physicians' attitudes and the state's attitudes towards care.***

"Erwin Liek and Karl Kotschau were two enormously influential physician-theorists who argued for the reorientation of care (and who) were radically altering the major goals of medicine.

"By minimising and even belittling clinical care of the individual…their argument entailed the manipulation of the very idea of care.

"Liek was a prolific and extremely popular writer who wielded enormous influence in the medical world of Germany and many other countries.

"Major responsibility for medical care shifts to the state, while the rationale for receiving care depends more and more on the individual's contributions to the state.

"Following Liek's death, (his disciple) Kotschau was still proclaiming –'almost with ideological obstinacy' – that medicine and people generally should turn away from their primary interest in disease, its treatment and cure (care of individual sick persons), and apply themselves to health, its promotion and preservation (ie. the needs of the entire society)".

Turning away from a primary interest in disease, its treatment and cure in favour of the commercial interests of "society" seems to be exactly in what the PACE Trial Chief Investigator, Peter White, is engaged, so it is worth reiterating his beliefs: *"some people believe that medicine is currently travelling up a 'blind alley' (and) that this 'blind alley' is the biomedical approach to healthcare. The biomedical model assumes that*

ill-health and disability is directly caused by diseases and their pathological processes" and **White posits that behaviour and the "social context" are an alternative approach to the biomedical model of disease** (Biopsychosocial Medicine, OUP 2005).

In his section "Moral commentary on the manipulation of care", Reich says:

"Understanding the betrayal of care: we can see that physicians and political leaders in National Socialist Germany accomplished a betrayal of care in three senses. First, they radically altered the very idea of care that constitutes the goal of medicine… subverting the moral standards of care in medicine. Second, they betrayed the actual care of tens of thousands of individual patients by violating the patients' trust in caregivers……And third, they betrayed the moral integrity of many physicians…by violating their sense of commitment to the interests, lives and health of their patients.

"In so doing, they deeply altered the ethos and ethics of medicine, simply by manipulating what it meant to care.

"The moral problem was that the deepest of medical sentiments in the service of the sick was distorted toward ideological goals to the total disregard of the individual.

"We see how vulnerable care is to societal and cultural forces: care itself can be perverted.

"The relative ease with which sentiments of care were manipulated to a global level of insufficient regard for the individual…could lead us to reflect on the extent to which we too easily overlook medicine's commitment to care for sick people and the apparent ease with which that commitment is betrayed.

"In the United States at present there is a gargantuan manipulation of the idea and commitment of care in the healthcare delivery system. ***'Managed care' has subjected care for the individual patient to the demands of commercial medical enterprises that take great care lest costs increase while profits decrease****. The major moral conflict of doctors in the United States today is this conflict between their responsibility to care for the best interests of the patient and their responsibility to take care of the system whose prime interest is in managing finances for corporate purposes.*

"We need to give more attention to care as the originary element of all ethics….For without care, all the patients' rights and all the professional rules and ethics codes imaginable will accomplish very little" (see also Section 3 below).

The socio-cultural factors that shaped the manipulation of medical care at that time seem to be re-emerging at the hands of UNUMProvident and the Wessely School in both the US and the UK.

For example, the PACE Trial seems to have no science behind it (the Wessely School studies that provide the alleged evidence-base for CBT and GET use the Wessely School's own Oxford criteria which exclude those with ME and rely on subjective questionnaires) and seems to be an exercise to remove people with the targeted disorder "CFS/ME" from State and insurance benefits, thereby subjugating the needs of the sick individual to the ideological goals of State and commercial interests.

With apparent contempt for the large body of evidence showing that ME/CFS is a devastating organic disorder, Waddell and Aylward assert:

"*Diagnosis is often non-specific…These conditions are 'characterised more by symptoms and distress than by consistently demonstrable tissue abnormality' and have been described as 'medically unexplained symptoms' to emphasise the limited nature of objective disease or impairment (Page & Wessely 2003)".*

Waddell and Aylward argue that the classic formulation of the sick role which entitles people to State benefits has *"major limitations"* because it is *"firmly rooted in a medical model of illness".*

"This approach is quite inappropriate and positively harmful for many common health problems that do not have any good medical answer. The traditional sick role can then become a trap, in which the patient continues futile attempts to find a medical solution.

"Conceptually, chronic pain, fatigue or comparable syndromes do not meet the criteria of severe and permanent impairments**. Pragmatically, it is impossible to set any threshold for severity, while the epidemiology and the North American experience show they could possibly lead to explosive growth. **For all these reasons, we would argue that they should not be regarded as severe and permanent impairments, but are better treated as potentially recoverable".

Then comes the possible explanation for the "eradication" of ME and the reclassification of CFS as a functional somatic (behavioural) syndrome: in order to qualify for benefits "*the illness must be recognised by a respected body of medical opinion and in practice, conditions which are specifically mentioned in major classification systems such as the ICD-10 or DSM-IV are very likely to be accepted as being 'clinically well recognised' ".*

In the Wessely School's syllabus, "CFS/ME" is a mental (functional somatic) disorder. From this it seems certain that if "CFS/ME" were to be formally re-categorised as a "mental" disorder in the major classification systems, the insurance industry would have cause to rejoice because, quoting Peter White, Waddell and Aylward say:

"*the insurance industry approach to total and permanent disability generally consists of … independent medical evidence that the claimant is suffering from a diagnosable functional disorder (and) the claimant has received at least two years of optimal medical treatment (OMT) by a recognised medical specialist. It is surprising how many claims fail to meet this criteria* (sic*). The commonest reasons for failure are that the consultant has not considered a biopsychosocial approach to rehabilitation".*

Common sense asks why an informed consultant would refer for psychotherapy a patient with a classified neurological disorder who is clearly incapable of work and thus under their policy entitled to PHI payment purely in order to convince the patient that s/he does not have a classified neurological disorder and is capable of work, especially given that Professor Trudie Chalder herself is on record as acknowledging that: *"Part of the problem of the BPS (biopsychosocial) model is that it is so broad and non-specific to render it almost completely meaningless. It is theoretic and it doesn't lead us anywhere"* (Biopsychosocial Medicine, OUP 2005).

The answer is to be found in the UNUMProvident literature (see Appendix IV) and in Waddell and Aylward's book:

"*There is good evidence from the insurance industry that it is often more useful to have the independent examination* (sic*) carried out by a doctor qualified in disability assessment medicine or by a non-medical health professional such as an occupational therapist or occupational psychologist".*

For the avoidance of doubt, the training of occupational therapists and occupational psychologists does not qualify them to assess complex neuro-immuno-vascular disorders such as ME/CFS.

In the same year that the book by Waddell and Aylward was published, on 22nd August 2005 another of the Woodstock attendees, Professor Derick Wade from the University of Oxford and the Rivermead Rehabilitation Centre, Oxford, wrote to Dr Roger Thomas, Senior Medical Policy Adviser in the Benefit Strategy Directorate at the DWP advising that – despite the WHO classification -- ME/CFS is not a neurological disorder but a ***"non-medical illness".***

When challenged about his views by the person about whom he had written, on 7th July 2006 Wade replied :

***"ME/CFS is not a neurological condition** in that there is no pathology in the nervous system.*

"The sick role does have advantages in that Society provides support to people who are ill…a not-inconsiderable advantage…

*"Why should all symptoms arise from disease…..Even if research such as that on the websites you gave does find abnormalities, it does not prove a causal link….**Why are so many people with ME so afraid of the idea that there is no pathology?…** I will end by re-stating that: I think that ME/CFS is a major problem for people with it and for Society but I do believe that: people with so-called ME/CFS do not have any disease as the primary or sole cause of their illness (and) **it is wrong to fit ME/CFS into a biomedical model of illness".***

Together with Professor Tim Peto (co-leader of the Oxford PACE Trial Centre), Professor Wade attended a meeting of the Oxfordshire Priorities Forum on 21st May 2008 at Jubilee House, Oxford Business Park South, the Minutes of which record: "*There is increasing evidence **from good quality trials** to support CBT and or GET in the management of CFS/ME (and) there is evidence for the effectiveness in children and adults…Inpatient care for CFS/ME is not supported by available evidence… **The Oxford PF agreed that GET and CBT are clinically and cost effective and should be recommended in the treatment of CFS/ME**".*

Strategies employed by the Wessely School to achieve their goal appear to include the portrayal of people with ME/CFS as malingerers. The frequency with which people with this illness are denied benefits and are forced to undertake a lengthy and stressful appeals process indicates that the Wessely School has been successful, even though the DWP's own Guidelines for DLA decision-makers states:

"*Between a quarter and a half of people with CFS/ME are in part-time or full-time employment or education. **When compared to people with other diseases like diabetes mellitus or arthritis seen in hospital clinics, many people with CFS/ME are on average more disabled**".*

This does not sound like people who are lazy or work-shy. Those who are able to sustain some employment whilst ill may sacrifice many other aspects of their life just to remain in employment. As the Countess of Mar noted:

"*In a recent national consultation with 1,162 ME sufferers, one of the correspondents wrote: 'The Government seem to think people actually LIKE to live their lives on benefits. The genuine claimants don't want to be on benefits but have no choice'. Why is it that I still get letters from acutely distressed people with CFS/ME who are being hounded by the DWP to attend interviews and who are threatened with loss of benefits if they do not comply?"*
(http://www.tinyurl.com/ygpf6hp).

The strategy of portraying people with ME/CFS as malingerers is extremely damaging to sick people who already experience prejudice, ignorance and medical arrogance; as Millen et al pointed out in 1998: "*Often CFS sufferers are stigmatised, or fear such labelling, as a 'malingerer' or are treated as having other psychological and somatic properties attributed to their 'undefined illness' "* (International Journal of Sociology and Social Policy 1998:18:7/8:127-147). These common experiences of patients do not accord with the Wessely School's notion that patients with "CFS/ME" are seeking sympathy, time off work, or other advantages of the sick role.

As the Gibson Inquiry's Report of November 2006 made plain: "*The lack of easy confirmation of the organic nature of the illness…lends itself to… invasion by those who are not genuine sufferers. **The existence of such patients and the inability of the medical profession to separate them from genuine patients with CFS/ME enhances the view that all patients with CFS/ME are neurotic and/or not genuinely ill**"* (http://erythos.com/gibsonenquiry/Docs/ME_Inquiry_Report.pdf).

On 10th September 2008 a conference entitled "Beyond Pathways to Work: health, work and well-being" was held at the Royal Society of Medicine. It was described as *"this important conference which follows three earlier successful conferences on Pathways to Work held by the Royal Society of Medicine in London and Cardiff during the past four years".*

Speakers included Professor Mansel Aylward CB, MD, FRCP and Aylward's successor at the DWP, Chief Medical Advisor Dr Bill Gunnyeon.

It must be remembered that Mansel Aylward is a member of the MRC PACE Trial Steering Committee.

Appendix III shows how the way may have been paved for the MRC PACE Trial and how it seems to be a vehicle for the implementation of UNUMProvident's policies.

The quotations in Appendix III illustrate just how impregnable is the meticulously constructed bastion of the biopsychosocial model of illness that seems to reduce organic disease to the category of myth by manipulating the concept of medical care to nothing more than corporate profit and wealth-earning potential for the benefit of commercial bodies and the State.

Backed by UNUMProvident and the Woodstock Group that, like the PACE Trial, was sponsored by the Department for Work and Pensions (where, it will be recalled, Peter White is the lead advisor on "CFS/ME"), it can hardly be denied that the Wessely School's efforts to eradicate ME and to re-categorise CFS as a mental disorder have been successful within the UK and far beyond.

Despite the then-Health Minister, Lord Warner, having confirmed in writing on 11th February 2004 that the Department of Health accepts that the correct classification for ME/CFS is WHO ICD-10 G93.3 (ie. neurological), in practical matters his letter seems inconsequential, because the "independent" agencies of State (the NHS, NHS Plus, the Centre for Reviews and Dissemination (CRD), the DoH, the DWP, NICE and the MRC) all regard and treat CFS/ME as a functional somatic (behavioural) syndrome, and CFS/ME remains on the NHS **mental health** minimum dataset, to which all NHS personnel must adhere.

In 2007 the Centre for Reviews and Dissemination produced a further updated systemic review of the treatment and management of adults and children with CFS/ME (CRD Report 35; University of York, July 2007) which asserted that there was: "*evidence supporting the effectiveness of CBT and GET in reducing symptoms and improving physical functioning*". **That systemic review was supportive of the broad criteria for "CFS/ME": "*The criteria inclusion for both the outcomes and interventions were broad, which was appropriate and allowed for a more comprehensive over-view of the available evidence*", with the CRD's own comment: "*This was a well-conducted and clearly reported review…conclusions are likely to be reliable*".**

Sadly, the conclusions are not likely to be reliable, because the patients studied in the review trials were not tightly defined, so could have included anyone who felt a bit tired.

Clearly ME/CFS sufferers seem to be battling not only a devastating disease and their ruined lives, but also a powerful and very extensive body of vested interests which works tirelessly to ensure that no-one will challenge the currently popular psychiatric paradigm (ie. that "CFS/ME" is a behavioural disorder).

That psychiatric paradigm, however, is believed by many to be wrong-headed; they believe it is unethical to "manage" patients with ME/CFS in the UK by means of ineffective and potentially harmful, non-evidence-based "rehabilitation" therapies that have apparently been discarded by mainstream international medicine and to offer nothing else, thereby abandoning large numbers of extremely sick people. The plight of people with ME/CFS in the UK is a travesty.

What is so appalling is that in 21st century Britain, people suffering from a devastating organic disease have evidence to show that they are denigrated, derided, mocked, bullied, harassed, coerced, threatened, deceived, overtly and covertly videoed, abused, subjected to injustice, denied their human rights, and effectively abandoned by the State to the extent that no appropriate investigations that might confirm their disease are permitted, all with the approval of the UK Government but at the apparent behest of a mammoth insurance industry whose objective is to maximise their profits.

Such is the influence of the Wessely School that it is unsurprising that a litigant in the High Court was told that Judges *"regard ME as psychological self-indulgence".*

From the evidence obtained under the FOIA, the outcome of the MRC PACE Trial may be expected to set such a belief in tablets of stone.

The UNUMProvident / DWP / Wessely School ideology must be compared with what Canadian ME/CFS expert Dr Byron Hyde said in 2003:

"Though ME/CFS usually represents significant disease processes, the underlying pathophysiologies causing these disease processes are so varied that it is unreasonable and perhaps even dangerous to suggest or embark on any uniform treatment.

*"**There has been an immoral intervention by the insurance industry into the philosophy of physicians and health workers treating this group of disease entities**. This corporate insurance company intervention has used the mechanism of sponsoring medical symposiums to produce a uniform insurance-friendly policy….negatively influencing other physicians who may not be aware of this economic relationship".* (The Complexities of Diagnosis. Chapter 3 in: Handbook of Chronic Fatigue Syndrome. Ed: Jason Leonard A et al. John Wiley & Sons, New Jersey, 2003; see also: http://www.meactionuk.org.uk/Organic_evidence_for_Gibson.htm).

As Hyde also says: *"All moderate to severe ME patients have one or more, and at times multiple…vascular dysfunctions….**The primary vascular change is seen in abnormal SPECT brain scans…(There is) cardiac irregularity on minor positional changes or after minor physical exertion, including inability of the heart to increase or decrease in speed and pump volume in response to increase or decrease in physical activity**….In many ME patients there is an unusual daytime tachycardia**….(There is) circulating blood volume decrease: this is a nuclear medicine test in which the circulating red blood cell levels in some ME patients can fall to below 50%, preventing adequate oxygenation to the brain, gut and muscles**….Vascular dysfunction may be the most significant causal basis of the multiple bowel dysfunctions occurring in ME….*

"Drs Jay Goldstein and Ismael Mena, using Xenon SPECT brain scans, demonstrated that the physiological brain function of an ME patient rapidly deteriorates after exercise. They also demonstrated that this physiological dysfunction could persist for several days following any of several stressors.

"Psychiatrists should not ever be placed in charge of diagnosis and treatment of ME patients. It is simply not their area of expertise and their meddling has at times caused great harm to ME patients.

"ME is always a serious, diffuse brain injury and permanent damage can be done to the ME patient by non-judicious pseudo-treatment" (Missed Diagnoses: Myalgic Encephalomyelitis & Chronic Fatigue Syndrome. Nightingale Research Foundation, 2009, ISBN 978-1-4092-7571-8).

(It should be noted that Dr Ismael Mena is one of the foremost worldwide experts in nuclear medicine and has received the Distinguished Scientist Award of the Western Chapter of the Society of Nuclear Medicine. It was as long ago as 1992 that he published evidence that a high percentage of ME/CFS patients have cerebral cortical hypoperfusion in the temporal lobes, and that the accuracy and reproducibility of these changes may demonstrate *"**primary inflammatory changes or secondary vascular impairment in these patients**":* Study of Cerebral Perfusion by NeuroSPECT in Patients with (ME) CFS. In: The Clinical and Scientific Basis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, 1992. Eds: Hyde B, Goldstein J, Levine P; Nightingale Research Foundation Press, Ottawa).

That the UNUMProvident / DWP / Wessely School ideology seems to have been bought wholesale by the British Government is a matter of utmost concern, not least because it is known to be driven by "policy-based evidence" rather than evidence-based policy.

Medical scientists and most clinicians know that symptoms are a signal that something in the body is wrong, and that symptoms are not merely *"bothersome bodily or mental sensations"* as claimed by Waddell and Aylward and as described in the Green Paper that preceded the Pathways to Work reforms.

The Wessely School social reformists have re-defined terminology to mean what they want it to mean. They seem intent on dis-empowering general practitioners, and the MRC PACE Trial seems to be part of this constructed "evidence".

Dr Suzanne Vernon, former ME/CFS researcher at the US Centres for Disease Control (CDC) but since 2007 Scientific Director of the CFIDS Association of America, stated on 5th December 2008 that there are now more than 5,000 peer-reviewed articles in the biomedical literature that tell us a lot about the disrupted biology of ME/CFS, about what happens to the immune and endocrine systems and to the autonomic and central nervous systems.

When asked why this information had not been harnessed, her reply was that there is no good reason why it has not been translated to the medical community, saying: *"no-one is filling that gap between the bench research and the bedside"*.

This is an important point: it is not that accurate information and knowledge are unavailable; it is that the information and knowledge are being systematically blocked by the extremely efficient and effective networking of the Wessely School who ensure that the gap between bench and bed is filled with their own views about "CFS/ME".

That networking also includes Wikipedia, which is one of the first ports of call for computer-literate people seeking information on the internet. Despite the seemingly false premise upon which the Wessely School model of "CFS/ME" is founded, it is their view which currently dominates; indeed, as noted by Alex Young (Co-Cure ACT: 7th September 2009), the Wikipedia entry now has a strong biopsychosocial bias, focusing on illness behaviour and mood disorders and on the alleged efficacy of CBT/GET. (A more accurate source of information about ME/CFS than Wikipedia is to be found on Disapedia: http://www.disapedia.com/index.php?title=Myalgic_Encephalomyelitis_(ME)).

Not only do the Wessely School flood the UK medical journals with their own beliefs about the nature of "CFS/ME", to the extent that it would take a brave editor to publish a contrary view (editors frequently publish highly uncritical assessments of CBT which focus on the few studies that support its use, whilst ignoring those controlled trials which did not find CBT to be effective and which warned about the dangers of exercising beyond physiological exhaustion), but the Wessely School also seem to have open access to major Australian and US journals and thus to an international audience. They also frequently publish in the medical trade journals which have wide circulation, and they seem to control to a large extent what is published about "CFS/ME" in the UK media seemingly through Wessely's involvement with the Science Media Centre (SMC), where he is on the Scientific Advisory Panel.

The SMC was set up in 1999 under New Labour to operate like a newsroom for national and local media when science stories hit the headlines, thus ensuring that only the Government's chosen "policy" about a medical or scientific issue is reported. The SMC provides "training days" for journalists as well as brainstorming sessions on ways to improve the communication of science through the media. It also provides off-the-record briefings with key figures at the centre of controversial issues who want to communicate with the media without being quoted directly. It is used by its Director Fiona Fox to promote the views of industry and to launch fierce attacks against those who question them. It is sponsored by the Royal College of Physicians, The Science Council, the drug company Pfizer and Merlin Biosciences, amongst others. The SMC website records Professor Simon Wessely as saying: *"We need to defend scientific expertise as a basis for sound policy decisions"*. Its website also states: *"Lucy Thorpe and her colleagues at Radio Five Live, and Professor Simon Wessely urged the SMC staff to find 'members of the public' to speak out for science"* (http://www.sciencemediacentre.org/uploadDir/536adminconsultation_report.pdf). It is the case that Health

Editors of broadsheet newspapers have confirmed that editorial policy will permit them only to publish items about ME/CFS that come from the SMC.

Other tactics used by the Wessely School to ensure dissemination of their own views have been unambiguously set out by Dr Tony Johnson (see Appendix I): *"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 the Healthcare Commission or NICE), Chief Medical Officers and Chief Scientific Advisors, or through public dissemination when the media picks up on…issues".*

It is public knowledge (and was announced at an International Research Conference – see above) that the Wessely School psychiatrists control the MRC; it is certainly the case that many of them sit on MRC Boards. In addition, the Wessely School travel the world giving presentations about "CFS/ME", for example, on the very day of the ME Research UK (MERUK) International Research Conference (25th May 2007) in Edinburgh (which not a single member of the Wessely School attended), Trudie Chalder delivered a lecture at St Olav Hospital, Trondheim, Norway, on Cognitive Behavioural Treatment for CFS/ME, which she extolled. As customary, Miss Chalder's views remain uninfluenced by the biomedical evidence that shows her beliefs about the nature of ME/CFS to be seriously misinformed. Wessely himself is apparently always available to the media: in its Notes for Editors, the online magazine "spiked" (which is militantly opposed to ME/CFS being accorded the status of an organic disorder) says that Professor Wessely is available for comment or interview and can be contacted through Sandy Starr at "spiked" (0207-269-9234).

The extremely effective network coverage by the Wessely School has thus filled the gap between bench and bed, but not with evidence-based knowledge.

In contrast to the Wessely School beliefs, Dr Vernon stated that ME/CFS is *"ultimately described as immune dysregulation and neuroendocrine disturbance"* and that ***"infection is the key to initiating/triggering ME/CFS and the immune system is central to sustaining (it). Hormones are critical in modulating the immune response. A unifying theme is disturbed cell signalling and cell metabolism.*** *We know that low cortisol occurs in some patients with ME/CFS. Cortisol is a critical molecule for regulating the HPA axis and is essential for modulating the immune response"* (http://www.prohealth.com/library/showArticle.cfm?libid=14167).

For the last four years the charity Invest in ME (IiME) has invited members of Her Majesty's Government and representatives of agencies of the State to attend their international Research Conference on ME/CFS held in Westminster. No-one has done so. The 2009 IiME Conference was held on 29th May but it was not until 1st July that IiME received a perfunctory response from the Prime Minister's Office in relation to a petition organised by IiME; the response provides further confirmation that the UK Government has no interest in the plight of ME/CFS sufferers.

Responding to the reply from the Prime Minister's Office, the Chairman and Trustees of IiME sent the following open letter to the Prime Minister (http://tinyurl.com/kvvhux).

"*The petition was a genuine attempt to engage your government and the organisations / officials which you fund with public money. It was an endeavour to provoke some understanding of the issues involved in the current policies towards ME research. The reply from your office is insulting in its complete lack of engagement of the proposal and of the underlying issues.*

"The MRC is a publicly-funded organisation 'dedicated to improving human health'. It should be accountable to the public. It is entirely appropriate for the Prime Minister to intervene when there is deliberate bias being operated by this 'independent' body which is, nevertheless, supposedly accountable to a government department.

"Both (the PACE and FINE Trials) are considered meaningless by ME patients and are ridiculed for their lack of scientific rigour in identifying true ME patients. Even those who have participated have criticised these trials.

"It is a scandal that the MRC causes prolongation of such an appalling waste of life and scarce resources; that it seems to lack any accountability for its actions (or lack of action); that it does not serve the patient community; that it is systematically flawed with a refereeing system for research proposals that is neither transparent nor fair; and that it ignores requests to attend a conference providing the latest information on biomedical research which is being held on its doorstep and which could lead to improvement in human health.

"We cannot comprehend why you and your ministers feel it 'inappropriate' to intervene to understand why the MRC policy towards research into ME is a failure.

"This is a pitiful response which is condemnable by its lack of up-to-date information and patent spin. It is symptomatic of a government which doesn't understand, doesn't bother to verify, and cannot be bothered to do anything.

"Your 'independent' MRC refused to fund world-class research from Dr Jonathan Kerr which is clearly seen by others abroad to be state of the art. Why is public funding for this valuable gene research constantly refused?

"If any of your government ministers or officials had bothered to walk the few hundred metres to the conference venue on 29th May this year then they would have been able to judge for themselves how fatuous the response from your office is.

"Quite simply your government's …attitude towards people with ME and their families is nothing short of scandalous.

"Invest in ME has, in its four years of existence, attempted to educate healthcare staff, the media and the public about the real situation with ME, and show the biomedical research which is being carried out and which holds promise of effective treatments. Consistently your government has refused to acknowledge any of this.

"Your government fails its citizens, refuses to take any action, ignores the effort of two and a half thousand people who petition you to help them, looks the other way to the plight of the hundreds of thousands of citizens affected by this terrible neurological illness and concentrates on spin and ignorance as the cornerstone of your policy toward ME.

"A year ago you gave a speech in which you stated: 'The NHS of the future will do more than just provide the best technologies to cure: it will also be an NHS that emphasises care. The NHS of the future will be one of patient power, patients engaged and taking greater control over their own health and their healthcare too'.

"We know of patients in the heart of London who suffer for years from ME and receive absolutely no medical treatment – lost voices with no recourse to help from a government and a healthcare service which provide nothing.

"It is easier for people in the UK with ME to get help to die than it is for them to get help to live – thanks to your government's policies.

"Your government's health ministers have consistently avoided taking any action, continued to answer letters from people with ME and their families by using outdated information, template paragraphs containing multiple inaccuracies and an indifference to the plight of chronically ill people.

"We ask you to let us take you to a chronically ill patient with ME so you yourself can see the utterly appalling situation which exists for people in this country who are denied treatments (which exist) due to the ignorance of the healthcare service, government ministers and establishment organisations responsible for deciding on which research is given funding. Will you now see the desperate need for action, meet with us and let us try one last time to make you understand what is really happening?".

Given the evidence that UK Government policy seems to be to refuse care of the individual with ME/CFS in favour of the corporate needs of the nation, it would be unwise to anticipate a positive response, especially given the Court of Appeal Judgment of 7th July 2009 that reversed the High Court Judgment of

Collins J who found that the UK Government had failed to comply with a European directive to protect people from the possible harmful effects of exposure to toxic chemicals; the reason given was that "*a balance needed to be struck between the interests of the individual and the community as a whole*".

Clearly, it seems that in the UK, the sick individual is now legally unimportant.

At the meeting on "ME and CFS" held on 11th July 2009 in the series "Medicine and me – Hearing the Patient's Voice" at the Royal Society of Medicine, Stephen Holgate, MRC Professor of Clinical Immunopharmacology at Southampton, spoke on "ME: a research orphan for too long".

His talk built on the presentation he gave in April 2009 ("Setting a new research agenda for CFS/ME") at the CFS/ME Clinical and Research Network Collaborative Conference held at Milton Keynes (an alliance mostly between the MRC and Government–funded charities including Action for ME and The Association of Young People with ME at which Professor Mansel Aylward was an invited speaker).

At the RSM, Professor Holgate said that ME/CFS has never really fallen into the neuro-scientific domain, but has been considered as a form of neurasthenia and as such was rejected by medicine, an image that has stretched to the present day; due to that history, there has been little research into the condition. He asked what has gone wrong, and why is not more known about ME?

He made the point that at the MRC, referees tend to reinforce the *status quo*, but the area of ME research needs to be opened up, as ME is a systems disorder and in 2009, for the first time, we are embracing complexity. **He said that "ME/CFS" covers 25 or more conditions but that the Government will not permit integrated research**. He said the new science is trying to apply new technologies. He talked about the "omics": genomics, proteomics and metabolomics.

Professor Holgate asked rhetorically how the ME situation could be improved, saying that it is necessary to get people involved in very serious science, and that he has tried to get the MRC involved in this: he spoke about his wish for an MRC inter-disciplinary group involving immunologists and neurologists, but then said that he was not sure if it would happen.

What Professor Holgate said about the MRC referees reinforcing the *status quo* would seem to indicate that the Wessely School's stranglehold on funding for biomedical research into ME/CFS will continue for as long as UNUMProvident continues to dictate Government policy about this devastating disease.

<u>The ignoring of patients' experiences</u>

No amount of behavioural therapy can feasibly reverse the pathology that has been shown to be present in ME/CFS, any more than "correct thinking" can cause an amputated limb to regenerate.

To support patients who must learn to live with life-wrecking diseases such as ME/CFS is one thing (and no-one could object to such support) but, despite their claims, this is not what is being offered to ME/CFS sufferers by the Wessely School -- what is being offered is restructured thinking, the aim of which is to correct what the Wessely School deem to be "*aberrant beliefs*" in order to convince patients that they do not suffer from an organic disease. As Wessely himself has confirmed, his form of CBT is directive, not supportive (see above).

There is no evidence that interventions that are informed by the Wessely School's theory are successful in ME/CFS. This is despite the fact that their theory has been in existence for over two decades and has been widely applied, including by Wessely himself. Anyone who discovers an effective intervention for ME/CFS will become instantly respected amongst patients and medical professional alike. Such acclaim for the Wessely School is noticeable by its absence.

Indeed, there is abundant evidence from numerous surveys by ME/CFS 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 ME/CFS 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 is thus an abundance of empirical evidence from ME/CFS patients and charities that GET can result in high rates of adverse effects.

Proponents of GET such as the Wessely School do not adequately inform people about these adverse effects and they dismiss the significance of these surveys by claiming that GET was not carried out under an appropriate specialist and therefore the harmful results can be discounted (see below). This is important, because if participants are not made aware of the risks, they cannot give informed consent.

The published version of the PACE Trial Protocol (http://www.biomedcentral.com/1471-2377/7/6, which is the version that was abridged in order to *"enhance communication for publication"*, the full version obtained under the FOIA consisting of 226 pages) states in the section "*Risks and benefits"* that *"There is a discrepancy between surveys of CFS/ME patient group members and published evidence from trials"* as the trial "evidence" suggests *"minimal or no risk with these treatments"*. In support of this statement, the Protocol cites two surveys which found GET made patients worse (Dr Lesley Cooper's 2000 joint MEA and AfME survey and AfME's own 2001 survey) and cites a further survey by AfME from 2003 (AfME Membership Survey 'Your experiences' questionnaire) as suggesting that deterioration following GET was *"related to either poorly administered treatment or lack of appropriate professional supervision".*

The "Invitation to join the PACE trial" leaflet builds on this same assertion: "*Some patient surveys suggest CBT and GET can make symptoms worse – but experts* (ie. the Wessely School themselves, who portray themselves as world-class experts in "CFS") *believe this happens when the therapy is not used properly or when there isn't good professional supervision".*

An editorial by Peter White et al in the British Medical Journal just after the NICE Guideline on "CFS/ME" was published (BMJ 2007: 335:411-412) further promoted this belief, claiming that: *"effective treatments are available"* and, quoting the NICE Guideline, CBT and GET *"show 'the clearest research evidence of benefit'".* White also cited what he claimed were two patient surveys carried out by Action for ME, one in 2001 (see above) and the other in 2004 ("All about ME: an introduction"). The latter reference in the BMJ appears to be incorrect, because it is not a survey; it is an AfME booklet that simply says about GET (on page 19): "*Surveys carried out by Action for M.E. suggest that graded activity / exercise can be harmful when misapplied".* It seems that Peter White may have meant to cite the 2003 AfME survey (reference 15 in the published version of the Protocol) when he asserted that the later survey *"showed that this was related to inappropriate advice or lack of therapeutic support"*, a declarative but unsupportable sentence, since an analysis of AfME's 2003 survey data reveals no supportive data for Peter White's assertion.

Furthermore, White seems amnesic about his own 1997 study referred to above (BMJ 1997:314:1647-1652) which was categoric: "*If patients complained of increased fatigue they were advised to continue at the same level of exercise*", which clearly disproves his claim that previous adverse events occurred "*when the therapy is not used properly or when there isn't good professional supervision*".

The short (published) version of the PACE Trial protocol states: "*We will also carefully monitor all participants for any adverse effects of the treatments".* If there is a need to monitor participants carefully, then there must be possible risks and participants were entitled to know about them and the researchers were obliged to inform participants of those risks. The 2003 survey by AfME appears to be used as justification for not taking the risks associated with GET seriously enough. Quite how the unsubstantiated suggestion of a charity that bears no responsibility for the safety of research participants is deemed to support the safety of the MRC PACE Trial GET participants is not made clear.

An e-BMJ response by ME advocate Annette Barclay (http://www.bmj.com/cgi/eletters/335/7617/411#176155) showed that what Peter White asserted did not withstand scrutiny: "*I was disappointed to see Peter White et al trying to put a 'spin' on a patient survey to cover up the very poor success rate of GET. The data from the second survey mentioned simply doesn't back up their claims. White et al said that the GET failures reported in the first survey were down to 'inappropriate advice or lack of therapeutic support'. However, the survey shows that the 2nd group who reported positive experience with GET were the group who had NO professional help at all. This shows White's argument about 'inappropriate advice or lack of therapeutic support' to be without foundation".* Annette Barclay also pointed out that Dr Lesley Cooper's 2000 survey reported that GET made people worse or was unhelpful in 61.3% of cases, and that the second survey carried out by AfME incorrectly referenced by Peter White in the BMJ did not use an independent survey company and did not ask the same questions as the earlier survey, yet of the 54 people who had undergone GET, 59% said that GET was either a negative or neutral experience. Her response continued: "*AfME did not ask how well people undergoing GET were supported by professionals involved and what difference this support made. They were not asked about 'inappropriate advice'. It's wrong of White to blame GET failures on these factors, rather than GET itself for people with ME".* Annette Barclay then delivered her punch line, pointing out that the second AfME (2003) survey found that: "*the worst type of professional for a person with ME to see was an Occupational Therapist, a Physiotherapist, or at a Gym. ALL the respondents who tried GET with an Occupational Therapist or at a Gym reported a negative experience. The Physios had more mixed results but many negatives….To sum up, the data does not support the spin given by White et al in their editorial. From the second survey, we know that the majority had a 'negative' or 'neutral' effect and that these were treated by professionals – the very people we rely on to give us 'appropriate advice and therapeutic support'".*

As Tom Kindlon pointed out on Co-Cure ACT on 11th September 2009, the large AfME 2008 survey (see above) found that there was no significant difference between the number of adverse reactions suffered by

those who undertook a programme of GET under an NHS specialist (31.1%) compared with those who undertook such a programme elsewhere (33.0%), which comprehensively demolishes the Wessely School's attempts to blame an "unauthorised" programme of GET.

Moreover, when on 18th April 2006 AfME's own Chair of Trustees (Trish Taylor) addressed the Gibson "Scientific Group on Research in ME at the House of Commons, she advised that: "*The AfME 2006 survey of over 2000 members indicated that 92% were made worse by physical activity*", and she recorded AfME's concern that GET remains the main source of "*evidence-based treatment*".

Furthermore, whilst the PACE Trial Chief Investigator (Peter White) acknowledges that "CFS" is a heterogeneous condition, he nevertheless believes that "treatment" must be homogeneous (ie. one size must fit all, as he made clear at the RSM meeting in April 2008).

Illustrations of patients' experiences of the Wessely School's management strategy

Long before the PACE Trial started, from the many disturbing instances in the "management" of people with ME/CFS (especially children and young people), there are some examples in particular that stand out.

(1) The case of Ean Proctor: perhaps the best-known case is that of Ean Proctor from the Isle of Man. Although his case is not directly related to the MRC PACE Trial, the person most involved with the forcible removal of Ean Proctor from his parents was Simon Wessely, who is in charge of the PACE Clinical Trial Unit and whose views about the nature of ME/CFS have not changed in the intervening two decades.

In 1988, a formerly healthy 12 year old boy named Ean Proctor from the Isle of Man had been suffering from ME since the autumn of 1986; his symptoms included total exhaustion, feeling extremely ill, abdominal pain, persistent nausea, drenching sweats, headaches, recurrent sore throat, heightened sensitivity to noise and light and loss of balance; he was also dragging his right leg. In 1987 his condition had rapidly deteriorated; he had gradually (not suddenly as may occur in hysterical disorders) lost his speech and was almost completely paralysed (which lasted for two years). He had been seen by Dr Morgan-Hughes, a senior consultant neurologist at the National Hospital in London, who had reaffirmed the diagnosis of ME and advised the parents that ME patients usually respond poorly to exercise until their muscle strength begins to improve; he also advised that drugs could make the situation worse.

Although he did not obtain his MRCPsych until 1986, during one visit by the Proctors to the National Hospital in 1988, Wessely (then a Senior Registrar in Psychiatry) entered the room and asked Ean's parents if he could become involved in his case; desperate for any help, they readily agreed. Wessely soon informed them that children do not get ME, and unknown to them, on 3 June 1988 he wrote to the Principal Social Worker at Douglas, Isle of Man (Mrs Jean Manson) asserting:

"*Ean presented with a history of an ability* (sic) *to use any muscle group which amounted to a paraplegia, together with elective mutatism* (sic). *I did not perform a physical examination but was told that there was no evidence of any physical pathology…I was in no doubt that the primary problem was psychiatric (and) that his apparent illness was out of all proportion to the original cause. I feel that Ean's parents are very over involved in his care. I have considerable experience in the subject of 'myalgic encephalomyelitis' and am absolutely certain that it did not apply to Ean. I feel that Ean needs a long period of rehabilitation (which) will involve separation from his parents, providing an escape from his "ill" world. For this reason, I support the application made by your department for wardship".*

Wessely's assertion that Ean suffered from elective mutism was subsequently shown in an EUA [examination under anaesthetic] to be untrue.

On 10 June 1988 Wessely provided another report on Ean Proctor for Messrs Simcocks & Co, Solicitors for the Child Care Department on the Isle of Man. Although Wessely had never once interviewed or examined the child, he wrote:

"I did not order any investigations….Ean cannot be suffering from any primary organic illness, be it myalgic encephalomyelitis or any other. Ean has a primary psychological illness causing him to become mute and immobile. Ean requires skilled rehabilitation to regain lost function. I therefore support the efforts being made to ensure Ean receives appropriate treatment". Under his signature, Wessely wrote "Approved under Section 12, Mental Health Act 1983".

In that same month (June 1988), without ever having spoken to Ean's parents, social workers supported by psychiatrists and armed with a Court Order specially signed by a magistrate on a Sunday, removed the child under police presence from his distraught and disbelieving parents and placed him into "care" because psychiatrists believed his illness was psychological and that it was being maintained by an "over-protective mother". Everything possible was done to censor communication between the child and his parents, who did not even know if their son knew why they were not allowed to visit him.

In this "care", the sick child was forcibly thrown into a hospital swimming pool with no floating aids because psychiatrists wanted to prove that he <u>could</u> use his limbs and that he would be forced to do so to save himself from drowning. He could not save himself and sank to the bottom of the pool. The terrified child was also dragged out of the hospital ward and taken on a ghost train because psychiatrists were determined to prove that he <u>could</u> speak and they believed he would cry out in fear and panic and this would prove them right. Another part of this "care" included keeping the boy alone in a side-ward and leaving him intentionally unattended for over seven hours at a time with no means of communication because the call bell had been deliberately disconnected. The side-ward was next to the lavatories and the staff believed he would take himself to the lavatory when he was desperate enough. He was unable to do so and wet himself but was left for many hours at a time sitting in urine-soaked clothes in a wet chair.

Another part of the "care" involved the child being raced in his wheelchair up and down corridors by a male nurse who would stop abruptly without warning, supposedly to make the boy hold on to the chair sides to prevent himself from being tipped out; he was unable to do so and was projected out of the wheelchair onto the floor, which on one occasion resulted in injury to his back. This was regarded as a huge joke by the staff.

In a further medical report dated 5th August 1988 for Messrs Simcocks, Wessely expressed a diametric opinion from that of Dr Morgan-Hughes, writing (barely two years after obtaining his MRC Psych):

" A label does not matter so long as the correct treatment is instituted. ***It may assist the Court to point out that I am the co-author of several scientific papers concerning the topic of "ME"….I have considerable experience of both (it) and child and adult psychiatry (and) submit that mutism cannot occur (in ME).*** *I disagree that active rehabilitation should wait until recovery has taken place, and submit that recovery will not occur until such rehabilitation has commenced……..it may help the Court to emphasise that…active management, which takes both a physical and psychological approach, is the most successful treatment available. It is now in everyone's interests that rehabilitation proceeds as quickly as possible. I am sure that everyone, including Ean, is now anxious for a way out of this dilemma with dignity".*

Ean Proctor was kept in "care" and away from his parents for over five months.

(2) <u>The case of Child X</u>: some ten years after her own nightmare experience, Mrs Proctor answered a knock at her door on the Isle of Man and was surprised to find herself confronted by a police officer who had been directed to question her by the Metropolitan Police. Although at the time she did not know it, another child with ME/CFS in southern England was being threatened with forcible removal from his home if his parents did not agree to his being admitted to a psychiatric hospital: in an effort to protect the child from

inappropriate treatment and medical harm, his father had surreptitiously taken him abroad. When police officers broke into the house, it seems they found Mrs Proctor's name and address and she was therefore suspected of assisting the boy's parents in his disappearance and of harbouring him, which was untrue. Believing his son to be safe, the father returned to the UK where he was arrested and sentenced to two years imprisonment, a sentence he was happy to endure, thinking that his son was safe. However, the child's mother was then targeted and threatened with imprisonment if the boy was not handed over to a particular psychiatrist at a Teaching Hospital. The physically sick child was forced to spend seven months under the "care" of this psychiatrist and was subjected to "active rehabilitation", during which time his condition deteriorated considerably. He became severely ill and terrified of health professionals. **The lengths to which some psychiatrists who have focused their careers on "eradicating ME" will go in order to obtain parental obedience, and the control they wield, is extremely disquieting.**

In 1998 Professor Wessely seemed to be curiously affected by elective amnesia over the compulsory removal of children with ME from their parents: his involvement with the wardship of Ean Proctor is incontrovertibly established, yet in a Channel 4 News programme on 26th August 1998 in which the case of Child X was being discussed, when asked by the presenter Sheena McDonald if there can ever be a case for the coercive approach in situations involving forcible removal of a child with ME from the parents, Wessely stated *(verbatim quote):* "*You know very well I know nothing about these cases"* and when Sheena McDonald asked: "*So you would agree that unless there is criminal abuse, there is never a case for a coercive approach to take children away from parents?",* Wessely replied *(verbatim quote):* "*I think it's so rare. I mean, it's never happened to me"*. Despite this denial on national television, there is unequivocal evidence that Wessely was personally involved in Ean Proctor's wardship and that he had advised the local authorities to take the action they did. On 13th September 1998 Wessely repeated on air his denial of personal involvement in the removal of children with ME from their parents (Child Abuse by Professionals; Brain Hayes; BBC Radio 5 Live).

As mentioned above, the "treatment" of sick ME/CFS children by certain psychiatrists who profess to specialise in "CFS/ME" was the subject of a Panorama programme ("Sick and Tired"), transmitted on 8th November 1999 and was profoundly disturbing (a videotape recording is available).

Nothing seems to have been learnt from the appalling case of Ean Proctor and there is no question that children with ME/CFS continue to be forcibly removed from their parents and home; this issue was raised by Dr Nigel Speight, a consultant paediatrician at the University Hospital of North Durham with 20 years experience of children with ME, who in April 1999 reported to the Chief Medical Officer's Working Group on "CFS/ME" that the frequency of psychiatrists diagnosing the parents of children with ME/CFS as having Munchausen's Syndrome by Proxy amounted to an epidemic and, a decade later, such atrocities are still occurring.

(3) <u>The case of a severely affected young man</u>: in a letter dated 22nd November 2003 the mother of a young man severely affected by ME wrote: *"The consultant in charge wrote to Dr Wessely for advice. On my son's hospital file is a document dated 07.03.01, a 'Draft Action Plan Proposal following consultation with Trudie Chalder'. I find the action plan shocking, and I was particularly disturbed by the penultimate paragraph, which states:*

*" '**We expect*** (her son's name) ***to protest, as well as the activity causing him a lot of pain. This may result in screams….it may feel punitive'.***

"This plan has never been discussed with me. There were a number of painful incidents…he was found bleeding from the stomach (and) had surgery in September 2001. On 18th April 2001 I wrote to the consultant about the pain my son must experience in having a naso-gastric tube frequently inserted…it had been re-inserted 11 times in the previous 7 weeks. I have no record of receiving a reply.

"The action plan also accounts for the diagnosis of 'elective mutism' (it will be recalled that thirteen years earlier, Simon Wessely claimed that Ean Proctor had elective mutism). *Community speech therapists have refused to work with him on the basis that he might 'not be compliant'.*

"There is a record of a confidential meeting on 31st May 2001, which agreed to continue with the behaviour programme. It states that: 'The Chronic Fatigue Service believe that this exercise programme is to pursue exercise to the point where he resists'. The service referred to above is the one at Kings College Hospital. I wrote to the consultant and complained that it was too much for my son. The response was to increase the programme further. I then discovered that in a referral letter, (the consultant) stated that my son was suffering from 'pervasive refusal syndrome'*. I complained to the Chief Executive of the Hospital Trust. An investigation was promised but this never happened.*

"(My son) was not being treated with any respect. ***I believe that the action plan devised by Trudie Chalder was harmful and posed unacceptable risks. The approach of Dr Chalder and the Chronic Fatigue Service is diverging from Department of Health policies like the Expert Patient programme. It is not good practice to cause patients 'a lot of pain' (and) I question whether it is ethical, indeed it may be unlawful.***

" ***Dr Chalder's position is extreme*** *and I hope the Department of Health will consider carefully whether it wishes the Chronic Fatigue Service, of which Dr Chalder is a member, to have any role in proposals for new services for patients with ME".*

It is notable that in his 9th Eliot Slater Memorial Lecture at the IoP on 12th May 1994, Simon Wessely said of Trudie Chalder: "*The range of talents involved in tackling this problem* (ie. those who believe they have ME) *is vast. This emphasises the multidisciplinary nature of the subject and also gives me an opportunity to acknowledge my collaborators…perhaps most of all Trudie Chalder and Alicia Deale who, alone amongst this range of talents, know how to help the sufferer".*

(4) The case of Sophia Mirza: there can be few people in the UK ME community who have not heard the results of the inquest into the tragic death from ME/CFS of 32 year-old Sophia Mirza from Brighton. Although severely sick with medically diagnosed ME/CFS, Sophia was abused by the doctors charged with her care by being wrongly sectioned under the Mental Health Act. Increasingly in cases of ME/CFS, the law which states that a person may be sectioned only if they represent a danger to themselves and / or to others is being swept aside by some influential but misinformed doctors involved with ME/CFS.

Sophia's mother, Criona Wilson, recorded:

"In July, the professionals returned - as promised by the psychiatrist. The police smashed down the door and Sophia was taken to a locked room within a locked ward of the local mental hospital. Despite the fact that she was bed-bound, she reported that she did not receive even basic nursing care, her temperature, pulse and blood pressure (which had been 80/60), were never taken. Sophia told me that her bed was never made, that she was never washed, her pressure areas were never attended to and her room and bathroom were not cleaned" (http://www.sophiaandme.org.uk/).

Although Sophia died in distressing circumstances in November 2005, the inquest was not held until 13th June 2006.

The first autopsy found no cause of death. Two weeks later, more tests were carried out and again, no cause of death was found.

Through the personal intervention of Simon Lawrence of the 25% ME Group for the Severely Affected (of which Sophia was a member) permission was sought for a further autopsy and -- unusually -- was granted by the Brighton Coroner.

This time, the examination of Sophia's spinal cord showed unequivocal inflammatory changes affecting the dorsal root ganglia, which are the gateways for all sensations going to the brain through the spinal cord. These inflammatory changes affected 75% of Sophia's spinal cord.

At the inquest, one of the pathologists stated: ***"ME describes inflammation of the spinal cord and muscles. My work supports the inflammation theory because there was inflammation in the basal root ganglia".***

Dr O'Donovan (the neuropathologist who, along with Dr Abhijit Chaudhuri, had examined the spinal cord) stated that psychiatrists were baffled by Sophia's illness, but that "*it lies more in the realms of neurology than psychiatry, in my opinion".*

Both Dr O'Donovan and the local pathologist, Dr Rainey, said that "ME" was the old-fashioned term and that new terminology --- CFS---has come in, so that was the term that would be used. Dr Rainey also gave evidence that Sophia had a "fatty liver".

In Sophia's case, the Coroner was specific: the medical cause of Sophia's death was recorded as: 1a) acute anuric renal failure; 1b) CFS. The second cause was recorded as including dorsal root ganglionitis. Sophia died as a result of acute renal failure arising as a result of ME/CFS. This is in keeping with the medical literature that shows end organ failure to be a common cause of death in ME/CFS.

Dr Rainey gave evidence that Sophia had a "fatty" liver. This is notable, because there are reports in the literature that enlargement of the spleen and liver in ME/CFS are not unusual. Published evidence shows infiltration of the splenic sinuses by atypical lymphoid cells, with reduction in white pulp, suggesting a chronic inflammatory process (see: Coincidental Splenectomy in Chronic Fatigue Syndrome. BJ Miller et al: JCFS: 1998:4(1):37-42). There are reports of hepatic involvement in ME going back to 1977:

"*Physical findings may include hepatitis*" (BMJ 21st May 1977:1350).

"*Enlargement of the spleen and liver is also not unusual*" (Rev Inf Dis 1991:13: (Suppl 1): S39-S44).

"*Typically, patients with major depressive disorder have no specific signs or symptoms. In contrast, (ME/CFS) patients have been reported to have a multiple findings, including hepatomegaly* (5 –20%)" (Psychiatric Annals: 27:5 May 1997:365-371).

In their evaluation of symptom patterns in patients with (ME)CFS who were ill for longer than ten years, Friedberg et al found hepatitis in 13.6% (J Psychosom Res 2000:48:59-68).

Mohamed Abou-Donia, Professor of Pharmacology, Cancer Biology and Neurobiology at Duke University Medical Centre, Durham, North Carolina, has published evidence to show that a combination of stress and chemicals results in trauma to the brain via a breaching of the blood brain barrier (BBB) and that stress can intensify the effects of some chemicals, making them very harmful to the brain, nervous system and liver, resulting in abnormal fatty deposits that diminish the ability of the liver to rid the body of toxic substances (Chemicals and stress damage brain and liver: Co-Cure RES / Ascribe Newswire, 26th February 2004; this evidence had been presented at the Sydney ME/CFS Conference in December 2001). Abou-Donia's seminal work provides evidence that organophosphate exposure produces apoptotic neuronal death and involves oxidative stress with a resultant neurodegenerative disorder (Arch Environ Health 2003:58:8:484-497).

(5) <u>A further illustration of the Wessely School's regime</u> is to be found in the case of a patient who developed ME/CFS and was admitted to The National Hospital, Queens Square, London. This professional person was under the care of a Wessely School psychiatrist who, when the patient lost his balance and fell over, simply laughed and walked away. This psychiatrist contacted the patient's fiancée and informed her that she should not visit the patient unless the sick man had walked up and down the corridor. The psychiatrist asked the patient why he kept manipulating those around him and he said to the patient words to the effect of "You'd better get out of bed – you don't want to spend the rest of your life in a long-term psychiatric unit". Ultimately, a member of staff contacted the patient's mother and advised her to remove her son from in-patient "care" because "bullying didn't work".

(6) Another, more recent illustration, is provided by a PACE Trial participant: *"**In desperation I even engaged in CBT via the PACE trial, which was quite obviously trying to manipulate the results and, if anything, was exacerbating my symptoms. I share the views of others that Wessely's comments are totally biased".***

(7) A further illustration confirms how patients attending the "CFS" centres are treated and comes from the Research into ME (RiME) website in 2006 (www.rime.me.uk/clinics-Sussex1.doc): ***"Not only are patients' needs not being met, these ill people are being brandished – bullied – intimidated in the most pernicious way, by the profession trained at the expense of the public purse".***

Other adverse comments, of which there are many, focus on the fact that patients are supplied with documents promoting the Wessely School's views but are never informed about the research showing that people with ME/CFS may be adversely affected by their interventions, particularly by GET.

Another issue often raised is that patients' relapsing physical symptoms are simply disregarded, with therapists not having the requisite medical knowledge to address them, yet assuring participants that symptoms can be reversed by exercise which, if they have true ME, is likely to be erroneous.

Illustrations of the effects of the psychiatric lobby's dissemination of misinformation

Just a few illustrations of the likely ramifications of Wessely School views are provided here.

The health writer for the web magazine "spiked" is Dr Michael Fitzpatrick, a GP and anti-ME activist well-known for presenting and promoting the views of Professor Simon Wessely and for his perverse and immoderate attacks on those with ME. One such article can be found at http://www.spiked-online.com/Articles/00000002D3B6.htm (SPIKED: Health: 17th January 2002: "ME: the making of a new disease"). Speaking in support of those with ME/CFS at the launch of his Working Group's Report, Professor Sir Liam Donaldson, Chief Medical Officer, said on the record: "*CFS/ME should be classed as a chronic condition with long term effects on health, alongside other illnesses such as multiple sclerosis and motor neurone disease*" (BBC News / Health: 11th January 2002: http://news.bbc.co.uk/1/hi/health/1755070.stm), only to be vilified by Fitzpatrick: ***"The CFS/ME compromise reflects a surrender of medical authority to irrationality. The scale of this capitulation is apparent when Professor Donaldson claims that CFS/ME should be classified together with conditions such as multiple sclerosis and motor neurone disease. The effectiveness of the ME lobby reflects its middle-class base."***

Supporting Fitzpatrick, Professor Michael Sharpe said in the BMJ that doctors would not accept a particular strategy just because the CMO's report recommended it (BMJ:2002:324:131).

From about 1987 onwards, the medical trade magazines (widely distributed free to doctors, especially to GPs and to hospital libraries by the drug companies) have made a point of mocking and denigrating sufferers from ME/CFS in a way they would not dare do about patients with multiple sclerosis or other neurological disorders and this has been reflected in the national media.

In April 1994 "GP Medicine" carried a bold banner headline proclaiming: "*GPs despise the ME generation*".

On 12th January 1995 "Doctor" magazine ran a feature called "Bluffer's Guide" by Dr Douglas Carnall entitled "*Yesteryear's neurasthenias*", in which he wrote "*Modern bluffers prefer the term chronic fatigue syndrome….if they really insist on a physical diagnosis tell them chronic fatigue syndrome is a complex disorder in which multiple biopsychosocial factors are mediated via the anterior hypothalamus --- in other words, it's all in the mind*".

On 5th May 1996, under the headline "Chronic Bandwagon Disease", CFS was described in the Sunday Express by Jonathan Miller as "Chronic Fictitious Sickness".

In February 1999 Adrian Furnham, Professor of Psychology at University College, London, suggested that there was a wealth of conditions that can be fashionable excuses for lack of success, writing in the Telegraph: "*You are not dim, or work-shy or lazy. No indeed, you are a chronic sufferer from a recently discovered syndrome! Indeed, this medical problem can probably account for all the setbacks you have met in life. Chronic fatigue. There is no cure, although reclining on a sofa watching 'Richard and Judy' is said to alleviate the worst symptoms"* (This was the subject of a complaint to the British Psychological Society, who decided that Professor Furnham had not committed any form of professional misconduct).

In 2000, "Doctor" magazine ran a quiz by Dr Tony Copperfield (known to be the pseudonym of a GP in Essex) in which GPs were asked to choose from four possible answers to the question *"What would be your initial response to a patient presenting with a self-diagnosis of ME?"* The correct answer was *"For God's sake pull yourself together, you piece of pond life"*. (This was the subject of a complaint to the General Medical Council).

On 23rd March 2001 in "GP" magazine Dr Marko Boganovic, a psychiatrist and research registrar, Merton College, Oxford, wrote about patients with CFS/ME: "*The provision of disability services and benefit payment is controversial because illness beliefs may be reinforced (and) services and benefits constitute secondary gain"*.

The issue of "*secondary gain*" is important. It is an often-repeated assertion by the Wessely School for which not a shred of evidence exists. Patients are desperate to get better and to resume their former lives and their independence. What "*secondary gain*" can possibly compensate for the loss of health, employment, financial security, social life and – far too often – the loss of home, partner, family and friends? If "*adopting the sick role*" and "*symptom amplification*" bring people with ME/CFS to the point of such despair that they consider or commit suicide, how can it be thought to be "*rewarding*"? The psychiatric lobby persistently fails to address this issue: at a conference held in London on 31st October and 1st November 2002 on the biopsychosocial model of illness, the question of secondary gain was raised, and Professor Michael Von Korff said: "*If we start with the assumption that (ME/CFS) patients are motivated largely by secondary gain….".*

To depend on such an assumption defies logic, so the question therefore needs to be repeated: where are the published studies which demonstrate that such patients obtain secondary gain? As Von Korff made plain, the psychiatrists' view is an assumption -- with reputations and careers being built on it -- but assumptions are hardly "evidence-based medicine" upon which Wessely et al purport to place such store (for a detailed report, see www.meactionuk.org.uk/PROOF_POSITIVE.htm).

On 20th October 2001 "Pulse" ran a series called "Choices for the new generation of GPs". The approach provided by Dr Mary Church (a Principal in a practice in Blantyre, Scotland and a member of the British Medical Association medical ethics committee) was particularly contemptuous but is not untypical: "*Never let patients know you think ME doesn't exist and is a disease of malingerers. Never advise an ME patient to make a review appointment".*

As noted above, early in 2002, at Wessely's instigation the BMJ ran a ballot asking doctors to vote on what they considered to be "non-diseases" that are best left medically untreated and Wessely is believed to have proposed ME. Along with freckles and big ears, ME was voted a "non-disease" and in April 2002 both broadsheet and tabloid newspapers ran banner headlines proclaiming that ME is a non-disease.

In March 2005, Dr Mike Jones, (Senior Physician at Edinburgh International Health Centre and Associate Specialist, Regional Infectious Diseases Unit, Western General Hospital), writing about Voluntary Agencies Medical Advisors, stated: "*In at least some cases of CFS, and possibly most, there are psychological factors…. Occasionally CFS is a clear benefit to the CFS patient in preventing the agency from posting the person to a location to which they do not want to go. Rational discussion …is often hampered by a polarisation by those who dislike*

psychological hypotheses of causation into 'believers' and 'non-believers'. Believers can dismiss the views that they do not like on the grounds that the person who holds those views 'does not believe in ME' " (http://web.archive.org/web/20050207023541/http://www.vama.org.uk/notes/2.php).

Twenty years ago, in 1989 when the UK charity ME Action Campaign (now Action for ME) represented those with ME as distinct from those with chronic fatigue, its journal Interaction carried the results of 1500 professionally conducted questionnaires that had been sent out and some of the responses are provided here.

Comments of doctors to ME patients:

- "Throw away your crutches – it's your head that needs them, not your legs"
- "Women of your age imagine aches and pains – are you sure you're not attention-seeking?"
- "I'm not prepared to do any tests, they cost money"
- "Shut up and sit down"
- "You are a menace to society – a pest. I wish you'd take yourself away from me"
- "You middle class women have nothing else to worry about"
- "Its one of those thing you silly young women get"
- "Hypochondriac, menopausal, you have the audacity to come here and demand treatment for this self-diagnosed illness which does not exist"
- "Stop feeling sorry for yourself – I have patients with real illnesses, patients who are dying from cancer"
- "ME is a malingerer's meal ticket"
- "Your inability to walk is in your mind"
- "I'm not going to further your career of twenty years of being ill"
- "Nothing at all wrong with this woman – Put her on valium" (to GP from Consultant).

Comments of ME patients about their doctors:

- "I was told I was lazy and laughed at"
- "(he said) the illness was a load of trollop, he laughed me out of the surgery"
- "(he) laughed when I told him I could only visit him if I felt fit enough"
- "I was called 'stupid' and shouted at on more occasions than I care to mention…one neurologist said he 'couldn't care less' whether I ever got better"
- "I was told I was a disgrace"
- "My illness started with a sudden, severe collapse. The doctor said that it was due to 'attention seeking'"
- "(I was) told that I was a nutter"
- " (I was) told I was selfish and introverted and it was nothing but hysteria"
- "(the) doctors said to me 'if you go on like this you will be struck off the register'"
- "(the doctor) said my symptoms / signs 'didn't exist'"
- "It was suggested 'a good man' was all I needed".

That same year, a severely affected female patient was informed by her GP that ME *"is a condition developed by the patient for what they can get out of it".*

On 10th July 2006 in his oral evidence to the Gibson Parliamentary Inquiry on ME/CFS, consultant physician and ME expert Dr William Weir pointed to a big problem – pervasive medical ignorance. He stated his belief that 90% of doctors believe ME/CFS is a psychiatric disorder.

ME/CFS patients continue to be accused by doctors of refusal to get better and of not wanting to work. In 2006 one patient was taunted: *"If you're able to get to my surgery, you're able to get a job. Don't confuse me with facts. My mind is made up"* (Co-Cure: 10th October 2006).

Another was sworn at and told she was abusing the NHS and ought to be ashamed of herself (this patient had worked in a senior clinical capacity in the NHS for longer than the GP concerned and was assessed by Social Services as requiring 24 hour care).

On 12th March 2008 Frank Furedi wrote about "*The seven deadly personality disorders. They used to be called the seven deadly sins: lust, gluttony, avarice, sloth, anger, envy, pride. With lust relabelled 'sex addiction' and gluttony turned into an 'eating disorder, it's no wonder Catholics are unsure about the seven deadly sins.* ***Sloth has been medicalised, too. The creation of conditions such as chronic fatigue syndrome invites people to make sense of their lassitude through a medical label***" (http://www.spiked-online.com/index.php?/site/article/4862/).

Unknown numbers of severely sick people with ME/CFS have been removed from GPs' lists, often with no prior warning. After the BMJ poll on non-diseases in 2002, one very sick ME patient was brusquely informed that "*This practice does not treat non-diseases*" and was removed from the list.

The tradition of shameful diatribes and invective against ME/CFS sufferers still abounds. Doctors seem to vie amongst themselves to produce jibes at ME sufferers' expense. Why do they not jibe with equal disdain and offence at those with other classified chronic conditions such as lupus or multiple sclerosis? The answer can only be because they have been encouraged to jibe at ME/CFS patients by decades of public denigration by the Wessely School.

That Simon Wessely is known to jibe at people with ME/CFS is a matter of record. For example, in his enthusiastic review of "Biopsychosocial Medicine" published by Oxford University Press in 2005 and edited by Peter White ("*Physicians with a keenness for epidemiology, sociology or psychology will treasure this collection")* Craig Jackson, Professor of Occupational Health Psychology at Birmingham City University, wrote about Wessely's Foreword: "*He almost completes it without a dig at the Chronic Fatigue fraternity – succumbing in the end"* (Occup Med 2005:55:7:582). That a professional colleague of Wessely should identify a pattern of mocking behaviour by Wessely towards such sick people, published without demur in a professional journal – thereby encouraging its acceptability – is a serious matter. It is especially serious given that Wessely is involved with *"advice about design and execution"* of a publicly-funded MRC trial involving the very people he is known to mock.

Sadly, it seems that this culture of contempt is set to continue and that the anticipated results of the PACE Trial will serve to perpetuate the climate of medical ignorance about ME/CFS because participants were selected using the Oxford criteria which identify people with a fatiguing illness but do not identify people with ME (see below).

The CCRNC Conference, Milton Keynes, 23rd April 2009

The CFS/ME Clinical and Research Network Collaborative Conference took place on 23rd April 2009 at Milton Keynes. Both the conference itself and the Network (now re-named the British Association for Chronic Fatigue Syndrome/ME and using the acronym "BACME") deserve mention.

The Chair of the CCRNC is Dr Esther Crawley, a consultant paediatrician who could be described as an ardent Wessely School supporter. On 8th July 2009 Dr Crawley spoke at the Countess of Mar's "Forward - ME" group meeting held at the House of Lords. The Minutes of that meeting and Dr Crawley's power-point presentation are accessible at http://www.forward-me.org.uk/8th%20July%202009.htm

Of particular note are the following points made by Dr Crawley:

- The CCRNC's own Constitution says it is a *"multidisciplinary organisation which exists to promote and support the delivery of evidenced based treatment for children, young people and adults with CFS/ME throughout the UK"* whose objective is "***To champion evidence-based approaches to the treatment of CFS/ME, such as those provided in the NICE guidelines****"* and which will use ***"clinical expertise to inform healthcare policy" and will "provide training for clinicians and researchers from all disciplines involved in the diagnosis and treatment of CFS/ME".***

- The CCRNC has an "*Active training programme"* and has *"the ability to provide national training programmes".*

- The CCRNC will ***"invite no more than four people drawn from National UK CFS/ME organisations which explicitly support the aims and constitution of the organisation to sit on the Executive committee as either observers or members".***

- Its research strength is that it has the *"largest cohort in the world".*

- Its strengths are "*working together -- 600 clinicians and researchers, MRC, NIHR (National Institute for Health Research), Welcome (sic), patient and carer reps, charity membership".*

It is particularly notable that the Minutes record that when asked by Dr Charles Shepherd, Medical Advisor to the ME Association, *"whether, in the light of the widespread opposition to the NICE Guidelines, charities that were opposed to them would be invited to become members or associates of the CCRNC executive*", Dr Crawley's response was: ***"In order to join the collaborative, charities would be expected to sign up to the evidence-based approach".***

The only possible interpretation of this is that patients' charities are welcome to participate provided that they accept the behavioural modification interventions of CBT/GET recommended in the NICE Guideline (for which Dr Crawley was a member of the Guideline Development Group) and provided they accept that "CFS/ME" is synonymous with "chronic fatigue".

Given the volume of biomedical evidence that does not support Graded Exercise Therapy it would appear that in this instance signing up to an "evidence based approach" involves signing up to an approach that ignores most of the evidence.

It has been ascertained that -- even though the CCRNC used the NHS logo on its documents and it is clearly closely associated with the NHS service provision for those with "CFS/ME", the network is unaccountable to anyone other than itself.

This would seem to be akin to medical totalitarianism, especially given that Wessely School "evidence-base" upon which the NICE Guideline is predicated has been so stringently criticised by international ME/CFS experts.

Science is not furthered by a self-reinforcing "collaborative" determined to exclude dissenting voices; rather, a vigorous and honest dialectic is required. Medicine has no place for cabals and the lazy thinking they foster.

The CCRNC has arranged conferences and workshops at which speakers included Professor Peter White; Professor Simon Wessely; Professor Trudie Chalder and others noted for their promotion of the psychosocial model of "CFS/ME", including Professor Mansel Aylward.

As noted above, Aylward was an invited speaker at the CCRNC conference on 23rd April 2009 and his presentation was especially disturbing. His 39 Power Point slides include the following extracts:

- *"The Power of Belief….Differentiating: Health Illness, Sickness and Disease…Social and Cultural Contexts…The Fatigue Syndromes"* (slide 2)

- *"The Psychosocial Dimension: How people think and feel about their health problems determine how they deal with them….**Extensive clinical evidence that beliefs aggravate and perpetuate illness and disability…Beliefs influence perceptions and expectations; emotions and coping strategies**; motivation"* (slide 5)

- *"**Illness, Sickness and Incapacity are primarily psychosocial rather than medical problems. More and better healthcare is not the answer**"* (slide 6)

- *"**Strengths of the BPS model: Places health condition/disability in personal/social context**"* (slide 17)

- *"A Way Forward: **Management…must address barriers to recovery….False beliefs – pivotal role**…Social factors – pervasive"* (slide 18)

- *"**Barriers to recovery and return to work are primarily personal, psychological and social rather than health-related 'medical' problems**"* (slide 29)

- ***"Chronic Fatigue Syndrome: Management: CBT and NICE Guidelines"*** (slide 35)

- ***"Promoting and Achieving Further Success: Believe that people can radically transform their behaviours with the right kind of impetus…Embrace the integrated bio-psycho-social paradigm shift"*** (slide 36)

In his slide 2, Aylward asserted: *"beliefs aggravate and perpetuate illness and disability"* but, as noted above, Epstein is clear: ***"the notion that cognition rules behaviour has not been adequately proven by any test"***.

Professor Aylward's presentation, like his publications referred to above, is not in accordance with the international biomedical evidence about ME/CFS and is a cause for serious concern.

Statements of Concern about CBT/GET provided for the High Court Judicial Review of February 2009

Over twenty renowned ME/CFS experts provided Statements in support of the Judicial Review of the NICE Guideline on "CFS/ME" heard in February 2009 in the High Court in London. Although they were specifically written in support of the challenge to the NICE Clinical Guideline on "CFS/ME", they express concern about the recommendation by NICE that the only management of ME/CFS should be CBT and GET, ie. the subjects of the PACE Trial.

Extracts from those Statements for the High Court include the following:

- *"In my view, the Guideline is biased and over rigid in its recommendations and will put a large number of ME sufferers at risk of harm through its strong recommendations for the use of CBT and GET. CBT is based on the idea that somatoform disorders are maintained by abnormal or unhelpful illness beliefs which lead to abnormal or unhelpful behaviour. The first requirement for a somatoform diagnosis is that there be no physical cause for the symptoms. This is not the case in ME/CFS"* (Malcolm Hooper, Professor Emeritus of Medicinal Chemistry, University of Sunderland, November 2007)

- *"Two forms of treatment…are CBT and GET. CBT is a psychological treatment. Its application in what is certainly an organic disorder is basically irrational. Its putative mode of action is based on the proposition that patients with ME/CFS feel unwell because they have an 'abnormal illness belief', and that this can be changed with CBT. It has never been proven to be helpful in the majority of patients with ME/CFS. GET comprises a regime of graded exercise, increasing incrementally over time. It has been almost universally condemned by most patient groups. A number of patient surveys have shown it to be, at best, unhelpful, and at worst, very damaging. Its application is counter-intuitive, particularly when one of the most debilitating and well recognised symptoms of ME/CFS is post-exertional malaise which can put some patients in bed for days after relatively trivial exertion"* (Dr William Weir, Consultant Physician, November 2007)

- *"The GDG has placed undue reliance upon a small number of RCTs that were methodologically flawed because they did not adequately define the patient population"* (Dr Terry Mitchell, formerly Consultant Clinical Lead (CNCC) of the Norfolk, Suffolk & Cambridgeshire NHS ME/CFS Service, 23rd June 2008)

- *"The predominance of psychologists / psychiatrists on the GDG is entirely inappropriate and has led to a biased analysis in my opinion. The GDG has placed undue emphasis on a few UK clinical trials which support the use of psychological treatments, however, these studies did not properly or adequately define their patient population"* (Dr Jonathan Kerr, Hon. Consultant in Microbiology; Consultant Senior Lecturer in Inflammation; Principal Investigator of the CFS Group, St George's University of London, 11th August 2008)

- *"You will see from my attached treatise that I consider that the recommendation of CBT and GET as blanket treatments of 'clinically excellent' first choice is extremely dangerous to patients. I am concerned that NICE claims that an adequate evidence base supports CBT/GET, when in fact the Guideline Development Group (GDG) relied almost exclusively on a handful of extremely controversial RCTs (random controlled trials). I have no doubt that patients in the research quoted by the GDG did not have ME/CFS"* (Dr Irving Spurr, Newcastle ME Research Group; 12th August 2008)

- *"My overall impression reading the Guidelines for the first time was one of alarm. I will limit my comments to the deficiency which has the greatest potential for harm to patients. The NICE Guidelines do not make any reference to the biomedical literature on ME/CFS. A physician who is new to the field and who has not had time to read the thousands of paper reporting measurable abnormalities in ME/CFS may get the impression that: (1) Biomedical issues are irrelevant in ME/CFS and that (2) CBT and GET actually make the core symptoms of people with ME/CFS better. A close read of the literature reveals that none of the core symptoms of ME/CFS improve with CBT or GET. The recommendation for GET stems from the often quoted but unproven assumption that deconditioning causes or exacerbates ME/CFS. In fact this assumption has been disproven (Bazelmans et al 2001; Harvey et al 2008) and cannot therefore be used as a basis for treatment. Informed consent is an ethical requisite in the practice of medicine. Informed consent requires that patients embarking on any therapy be told the potential benefits and risks of the therapy being recommended. Meeting this legal standard in ME/CFS requires that patients be told about the potential benefits and risks of CBT/GET. If patients are being coerced to believe what is not true, psychological trauma can result. If patients are pushed to increase activity beyond their capabilities, exacerbation of symptoms can be expected. The NICE Guidelines are biased towards a particular model of CBT/GET that is widely viewed as ineffective and potentially unethical"* (Dr Eleanor Stein, Psychiatrist, Alberta, Canada, 12th August 2008)

- *"(Graded exercise therapy) is not therapy – it is simply the enforcement of an opinion rather than a treatment based upon any scientific examination of a patient's pathology and treatment of that pathology. I believe that those who developed (the) graded exercise programme as a valid treatment of ME have already been soundly criticised to the Courts. I also believe scientific evidence that such a programme is against the best interests of ME patients has already been presented. The benefit of such a programme is to the interests of the insurance industry and not the patient. Graded exercise programmes may be significantly dangerous to*

many of these ME patients" (Dr Byron Hyde, Clinician specialising in ME, having examined over 3,000 patients between 1984 – 2008; Ottawa, Canada; 15th August 2008)

- *"(The GDG) produced a Guideline that recommends CBT and GET as the prime treatment yet there is in fact published evidence of contraindication / potential harm with GET. This has been published by independent researchers (e.g. Peckerman et al). The NICE GDG claims that CBT/GET are supported by significant research. In fact the GDG relied almost exclusively on specious reports which are unproven"* (Dr Derek Enlander, Virologist specialising in ME/CFS; formerly Assistant Professor at Columbia University and Associate Director of Nuclear Medicine at New York University; Physician-in-Waiting to the UK Royal Family and to members of HM Government when they visit New York; 18th August 2008)

- "*I regard the continuing aura of disbelief surrounding the illness and mainly emanating from the psychiatrists as detrimental to both medical progress and the interests of sufferers"* (Dr Nigel Speight, Consultant Paediatrician specialising in ME/CFS; 20th August 2008)

- *"It is with regret that I note that the NICE Guidelines do not take into account recent developments in the management of ME. They lean towards a psychological and psychiatric basis, when it is now recognised that there are a large number of medical problems associated with ME. Recent studies on genetics, the central nervous system, muscle function and persistent infections have shown that there is a great deal of medical information available with regard to the management of ME"* (Dr Terry Daymond, Consultant Rheumatologist and recently Clinical Champion for ME for North-East England; 22nd August 2008)

- *"Research from the 'organic school' identified many pathophysiological abnormalities in patients with ME/CFS resulting from dysfunction in a number of vital control systems of the body such as the central nervous system, the autonomic nervous system, the endocrinological system and the immune system. The attitude of the 'psycho-social' school continues to be to largely ignore this research. It seems they can only maintain their hypothesis by discouraging the search for an organic basis and by denying the published evidence, which they are certainly doing. This unseemly battle of ideas has been settled politically by proclamation and manipulation, not by science, and not by fair and open means. CBT and GET appear to be based on the rationale that patients with CFS/ME have 'faulty' belief systems concerning the 'dangers' of activity, and that these aberrant beliefs are significant perpetuating factors. If CBT to 'correct' these 'false' beliefs can be combined with a graded exercise programme to re-condition these patients, it is virtually promised that a significant proportion of them will improve both their attitude and their physical functioning, and thus cure their illness. Using CBT, patients are therefore to be challenged regarding their 'aberrant' thoughts and expectations of relapse that the 'psycho-social school' psychiatrists believe affect symptom improvement and outcomes. Cognitions concerning fatigue-related conditions are to be addressed; these include any alleged 'over-vigilance to symptoms' and reassurance-seeking behaviours, and are to be dealt with using re-focusing and distraction techniques. It is when a therapy such as CBT begins to interfere with the natural warning systems, of which both pain and fatigue are a part, that the increased risks arise. In particular, musculo-skeletal pain and fatigue have essential function in modulating activity when the body is in a state of disease as in ME/CFS. NICE, however, recommends over-riding this essential safety-net, thus the risk of serious harm is increased in this situation of simultaneous activity and symptoms denial. This will become a more serious risk in patients with more severe ME/CFS. The Guideline does not indicate how the clinician can tell whether patients' beliefs concerning their symptoms are aberrant and/or when the symptoms accurately point to the underlying state of the disease process"* (Dr Bruce Carruthers, Consultant Physician, Vancouver, Canada, 29th August 2008)

- *"There have been only five trials of CBT with a validity score greater than 10, one of which was negative for the intervention; and only three RCTs of GET with a validity score greater than 10. The total number of available trials is small; patient numbers are relatively low; no trial contains a 'control' intervention adequate to determine specific efficacy, and their results are relatively modest. In addition, some of the studies (particularly those on GET) have used the Oxford criteria for diagnosis, a rubric which allows selection of*

*patients with chronic fatigue states and which do not necessarily exclude certain psychiatric disorders, raising the question of the applicability of the results of these studies to the many patients with specific biomedical symptoms and signs consistent with myalgic encephalomyelitis. Again, the heterogeneity of the trials, the potential effect of publication or funding bias for which there is some evidence, and professional doubts about the evidence base for some behavioural therapies themselves give grounds for caution as regards the usefulness of (CBT/GET). A commentary in the BMJ (Bolsover 2002) is particularly relevant: '**Until the limitations of the evidence base for CBT are recognised, there is a risk that psychological treatments in the NHS will be guided by research that is not relevant to actual clinical practice and is less robust than is claimed'**. Indeed, a large body of both professional and lay opinion considers that these essentially adjunctive techniques have little more to offer than good medical care alone"* (Dr Neil Abbot, Director of Operations, ME Research UK; Hon Research Fellow, Department of Medicine, University of Dundee, 29th August 2008)

- *"The overall flavour of the Guideline is to lump together all patients with 'medically unexplained fatigue', from relatively mild to profoundly disabling illness and to treat all patients with a standard approach of gradual reconditioning and cognitive behavioural modification. By lumping such a heterogeneous mix of patients…patients with CFS or ME are left with very limited options, and little hope. In addition, this document proscribes immunological and other biologic testing on patients with (ME)CFS in the UK, despite the evidence in the world's medical literature that such testing produces most of the biomedical evidence of serious pathology in these patients. Equally unfortunate is the GDG's recommendation for behavioural modification as the single management approach for all 'medically unexplained fatigue'. **This month we participated in the International Conference on Fatigue Science in Okinawa, Japan. Dr Peter White of the UK presented his work using behavioural modification and graded exercise. He reported a recovery rate of about 25%, a figure much higher than seen in US studies in (ME)CFS and, even if possible, simply not hopeful enough to the 75% who fail to recover"*** (Professors Nancy Klimas and Mary Ann Fletcher, University of Miami; 13th September 2008)

- Attached as an appendix to the Statement of Professors Klimas and Fletcher was a separate Summary of Current State of Understanding of (ME)CFS), from which the following quotations are taken: *"Many of the symptoms of (ME)CFS are inflammatory in nature. There is a considerable literature describing immune activation in (ME)CFS. Overall the evidence has led workers in the field to appreciate that immunologic abnormalities are a characteristic of at least a subset of (ME)CFS and that the pathogenesis is likely to include an immunologic component. Fulcher and White (2000) suggest a role for deconditioning in the development of autonomic dysfunction and overall level of disability in (ME)CFS patients. On the other hand, Friedberg et al (2000) suggest the long duration (ME)CFS subjects are more likely to have symptoms suggestive of chronic immune activation and inflammation. We are currently working with investigators at the Centres for Disease Control and the University of Alberta looking at the mediators of relapse after exercise challenge using gene expression studies, neuroendocrine, immune and autonomic measures"*

- *"My main concern about the NICE document is that what must be great uncertainty in both costs and particularly in quality of life difference is not allowed for"* (Martin Bland, Professor of Health Statistics, University of York, 17th September 2008)

- *"The guideline is dominated by positive and largely uncritical recommendations for CBT and GET. However, the guideline plays down the fact that patient experience has consistently reported that significant numbers of people with ME/CFS find these approaches to be either unhelpful or, in the case of GET, makes their condition worse. Some of the hospital-based services are not being physician-led but 'therapist-led'. In some cases people are now being given little more than a 'therapist-led' management assessment followed by an offer of CBT and/or GET. I received some very unhappy patient feedback on this type of service on Saturday 11th October (2008) in Colchester, Essex, where great dissatisfaction was expressed by many members of the audience who attended the ME Association's 'Question Time' meeting"* (Dr Charles Shepherd, Medical Advisor, ME Association, 24th October 2008)

- *"I am a consultant immunopathologist and before retirement worked at St James' University Hospital, Leeds. A key area of my professional interest was and remains myalgic encephalomyelitis and I have carried out research into the disorder. For a number of years I ran clinics specifically for patients with ME. In my opinion NICE guidelines overemphasise the usefulness of CBT and GET to the detriment of patients. I have no hesitation in stating that in my opinion, the situation for ME/CFS patients is worse, not better, since the publication of the NICE Guideline"* (Dr Layinka Swinburne, Leeds, 22nd October 2008)

- *"As my clinical freedoms were progressively eroded, it meant that I was becoming ineffective and indeed possibly dangerous as a practitioner. All that patients could be offered was CBT coupled with GET, which I consider not to be appropriate for many of my patients and in the case of GET potentially damaging for some"* (Dr Sarah Myhill, General Practitioner specialising in ME/CFS, Powys; Secretary of the British Society for Ecological Medicine, 10th November 2008).

Unfortunately the High Court Judge before whom the unsuccessful Judicial Review of the NICE Guideline on "CFS/ME" was heard (Mr Justice Simon) remained unmoved by these Statements and it is not known if he even read the ones that were provided for him.

They were certainly not mentioned in Court and there is no mention of them in the official transcripts or the Judgment, and CBT/GET remain the national "treatment of choice" for people with ME/CFS.

Seemingly untroubled by actual evidence, the Wessely School and UNUMProvident's control over the lives of ME/CFS patients and their families continues unabated.

For UK agencies of State to be involved with a company with the public track record of UNUMProvident, especially given the number of legal judgments against it, ought to be a matter of pressing disquiet for those in Government, but all attempts to bring these legitimate concerns to the attention of Ministers have been ignored.

UNUMProvident has been found guilty in numerous high profile legal cases of unwarranted delays in the processing of claims and of wrongful denial of claims, resulting in awards of punitive damages against the company for its improper refusal to pay legitimate claims, for example:

- In a claim against UNUM brought by Dr Joanne Ceimo (who was unable to work as a cardiologist following a neck injury), UNUM faced $84.5 million damages for "*mistreating an injured policy holder*", including $79 million in punitive damages. Dr Ceimo's lawyers said that evidence from previous policyholder cases against UNUM helped pave the way for this verdict

- In another case against UNUM, Judge O'Malley Taylor criticised UNUM, saying: "*There is clear and convincing evidence that (UNUM's) bad faith was part of a conscious course of conduct firmly grounded in established company policy"*

- A federal lawsuit filed in New York sought to represent tens of thousands more UNUM policyholders as part of a class action against the company, and in another case, the State of Georgia recently fined UNUM $1 million over its claims handling practices

- UNUM's own former medical director, Dr Patrick Fergal McSharry, has filed a lawsuit against the company, claiming that the company's "*primary purpose and policy*" was to deny disability claims

- He also stated that company medical advisers were encouraged to use language in their reports that would support claim denials, and that if too many medical opinions favoured the policyholder, the doctors would be reprimanded or sacked

- Another UNUM policyholder, Accident and Emergency physician Dr Judy Morris, discovered that her claim had been denied due to the input of Professor Michael Sharpe's "evidence" that ME/CFS is a psychiatric disorder (upon which UNUM apparently relies to support its stance that psychological rehabilitation regimes will cure ME/CFS, which is apparently the basis upon which UNUM relies to deny ME/CFS disability claims). When she contacted him, Dr Morris received an email from Sharpe telling her that UNUM's employees were not the "monsters" she was making them out to be

- In November 2004 The New York State Insurance Department reached a settlement with UNUM Provident: the company agreed to a fine of $15,000,000. On pages 12-15 of the February 2005 issue of "ME Essential", the magazine of the UK ME Association, the Association's Medical Adviser wrote about this case: *"UNUMProvident Corporation has agreed to re-assess more than 200,000 disability claims it originally denied since 1997 (in order) to settle (an) investigation (that) included a $15 million fine (for) unfairly evaluating the medical conditions of people making a disability claim (and for) relying too heavily on in-house medical staff to deny, terminate or reduce insurance benefits"*

- The same article noted that in the UK, *"when a dispute arises over eligibility, doctors called in to conduct disability assessments often have a close and regular financial association with the insurance industry. It is not acceptable for the insurer to interfere with or take control over medical management. There are certain types of medical experts who are very happy to do insurance work. Such doctors tend to support the view that many ME sufferers are malingerers. Needless to say, certain doctors have been extensively supported by the insurers and the names of these psychiatrists appear repeatedly"*

- On 4th April 2005, respected international expert in ME/CFS Professor Charles Lapp from Duke University, Charlotte, North Carolina, chaired a meeting of the ME/CFS Advisory Committee on Disability Issues; tactics used by the insurance industry to deny claims were identified as: (i) relentless harassment of claimants; (ii) threats to claimants; (iii) covert surveillance of claimants; (iv) unlawful interference with the mail of claimants; (v) denial of legitimate claims --- not paying claims, regardless of merit, no matter what proof is provided; (vi) claimants forced into legal action when they are too ill to launch an appeal; (vii) delays lasting years in processing legitimate claims; (viii) arbitrary termination of claims; (ix) habitually ignoring pertinent, objective medical evidence that supports a claim; (x) claimants subjected to years of systematic slander, victimisation, ridicule, harassment and acts of terror; (xi) changing the diagnosis to mental illness under duress to allow insurers to terminate benefits; (xii) employing company doctors who have no appropriate knowledge or clinical experience of ME/CFS

- In one High Court action in the UK, UNUM employed private investigators over a period of eleven years but still had no evidence to offer, which the Judge thought remarkable

- In September 2005, the Book Review Section of the New York Times (NYT) featured a book that had just been published about UNUM's disability claims abuses ("Insult to Injury: Insurance, Fraud, and the Big Business of Bad Faith" by attorney Ray Bourhis; Berrett-Koehler Publishers, Inc., SF). The item in the NYT Book Review stated: *"Joan Hangarter trusted UNUMProvident --- until she became disabled and consequently found herself and her children broke and homeless after UNUMProvident terminated her claim, cancelled her policy and stopped paying her benefits she was rightfully owed. (She) won a landmark $7.7 million jury verdict against UNUMProvident. Bourhis uses (this) story and the stories of others to expose how insurance companies get away with denying valid claims, terminating benefits, and destroying people's lives"*

- Because it cannot be free from corporate interests, UNUM's official association with UK Government bodies may inevitably place its corporate interests above the welfare of those in the UK claiming sickness and disability benefits (because it has direct financial interest in securing cutbacks in State sickness and disability benefits)

- Disability insurance policy requirements increasingly imply the requirement for a claimant to participate in a "physical rehabilitation" regime for the duration of a claim, and that disability benefits may be terminated if a claimant refuses to take part in such (Wessely School) "rehabilitation" regimes.

The UK Departments of State and the frequently-changing Ministers of those Departments seem to remain either unknowing, unperturbed or uncaring, so people with ME/CFS continue to be targeted and they remain victims of the State which continues to follow UNUMProvident's policies in respect of ME/CFS.

For more information about UNUMProvident's involvement in the UK health service and the PACE Trial, see Appendix III.

The refusal of the Wessely School to heed the biomedical science is causing increasing concern.

Last year's winner of the Nobel Prize in Medicine, Professor Luc Montagnier of France, who was one of the discoverers of the HIV (AIDS) virus, says of ME/CFS: "***Scientists have already uncovered a lot about ME, but this information does not reach professional healthcare personnel, and the disease is still not taken seriously. It is about time this changes"*** (ESME [European Society for ME] Press Release for conference in Stavanger, Norway, on 13th June 2009: Experts launch Think Tank for Mystery Disease).

That concern also pervades the UK. On 5th June 2009, commenting on a letter published in the UK Bristol Evening Post about ME/CFS, Hilary Patten wrote:

"*ME has been classified as a neurological illness by the WHO since 1969, and the UK Government have stated that they accept it is a physical illness. Despite this, all research and treatment funding has been given to the psychiatric profession who insist, against all medical evidence, that it is an 'aberrant illness belief'. Sufferers are mixed up in CFS clinics with patients who have a number of different fatigue-causing illnesses, including mental disorders, and given totally inappropriate psychological treatments that have been found by all patients groups to actually make them worse. This is a dreadful waste of taxpayers' money that could have been spent on biomedical research. There have been a number of deaths from ME in which pathogens have been found in the heart, central nervous system, gut and muscles at autopsy. Recent research has found a previously undiscovered prion in these profoundly affected patients. Until the UK psychiatric profession release their stranglehold on this physical illness there will never be effective treatment for ME in the UK. ME sufferers desperately need a diagnostic test to be developed. This needs funding to be redirected away from the endless and useless psychiatric research and put into biomedical research".*

Ms Pattern kept up the public pressure: referring to reports that Conservative Member of the European Parliament Daniel Hannan made in America about the shortcoming of the British NHS (the world's third largest employer after Indian rail and the Chinese army), where Mr Hannan said he *"wouldn't wish it on anybody"*, particularly its queuing, rationing and bureaucracy, on 16th August 2009 she wrote to The Times:

"*The quarter of a million sufferers of myalgic encephalomyelitis (ME) in this country, who can access no effective NHS treatment for their physical illness, might agree with Mr Hannan in that they would not wish their NHS 'care' on anybody. Instead of receiving biomedical treatment, ME sufferers are mixed up with sufferers of other fatigue-causing conditions. All UK taxpayers' research and treatment millions have gone to the psychiatric profession that insist, against all scientific evidence, that it is an 'abnormal illness belief'. The parliamentary Gibson report recommended that these psychiatrists be investigated for a possible conflict of interest in also working for large insurance companies. This has never been done. Is healthcare here also, in President Obama's words,'working better for the insurance companies' than for ME sufferers?".* The answer is an unequivocal "yes".

The presentation by Catriona Courtier at the Royal Society of Medicine meeting in the "Medicine and me" series on 11th July 2009 emphasised the scandalous situation faced by ME/CFS patients in the UK:

"Over the twenty years I have had this illness, what has really bedevilled the situation of patients with ME has been the belief, which has been persistently promulgated, that we are suffering, not from a physical illness but from an illness belief. This is at the root of all the problems we experience: the lack of resources, the hostility and disbelief from some doctors, the ignorance and disinterest in our symptoms, the ineffective treatments, the harmful treatments and in the very worst cases, the imposition of psychiatric treatment against the patient's wishes.

"In 2002 the working group of the Chief Medical Officer said 'ME is a chronic illness meriting significant NHS resources'. However, in the same year, an editorial in the Journal of the Royal College of General Practitioners questioned the validity of the CMO's report. It described patients with ME as suffering from PUPS, persistent unexplained physical symptoms and said: 'illness belief and behaviour do not amount to proof of physical causes and there are gains involved in adopting victim status' .

"At that time, studies had shown reduced blood flow to the brain, decreased uptake of acetylcarnitine in the brain, increase in choline in the brain, abnormalities in muscle mitochondria and so on. Since then we have had research showing increased levels of cell death and research in London and Glasgow by Dr Kerr and Dr Gow using gene expression which has shown upregulated genes in patients with ME. In spite of this I have been told by a consultant physician who sees many patients with ME that ME is by definition an illness where there is nothing physically wrong with the patient.

"One of our members was treated in a leading specialist clinic in a London hospital. Her GP was informed that she was making good progress. He was told that the only problem that remained was her 'illness belief'.

"Those who promulgate the view that ME is an illness belief have undermined the mutual trust and respect that should exist between doctor and patient. They have done a great disservice to both patients and to the medical profession.

"The latest research I have seen was in 2008 by Neary et al in the Journal of Clinical Physiology. This reproduced earlier research using SPECT scans which showed that blood and oxygen supplies to the brain of subjects with ME decrease rather than increase after exercise. In spite of this the patients in west London in the specialist clinic this year have been given material which says that their symptoms are due to lack of fitness and can be reversed by exercise*. The only negative effect they are told about is muscle stiffness which is described as a normal strengthening of the body.*

" No explanation is given of the malaise, digestive upset, headaches, nausea, sleeplessness and myriad other symptoms that people with ME experience after exercise. Patients are told there is nothing to stop their bodies gaining strength and fitness.

"I began by describing the severely affected as the weakest among us. In some ways they are the strongest. If people climb mountains or sail round the world single-handed they are praised for it, but to live for many years with an illness like ME is also a huge feat of human endurance and courage but is seldom recognised as such. People with ME at all levels deserve to be respected. They deserve to be listened to".

That patients with ME/CFS continue to be neither listened to, appropriately investigated nor correctly cared for but effectively abandoned is believed by many to be the shameful legacy of the Wessely School, and the MRC PACE Trial seems to be part of that legacy.

The reference in Mrs Courtier's presentation was to the particularly disturbing Editorial in the JRCGP in May 2002 ("Doctors and Social Epidemics: the problem of persistent unexplained physical symptoms, including chronic fatigue" by Ian Stanley, Emeritus Professor of General Practice; Peter Salmon, Professor of Clinical Psychology, and Sarah Peters, Lecturer in Psychiatry, all from the University of Liverpool) which claimed that "CFS/ME" is a "social epidemic". Dismissive of the Chief Medical Officer's Working Group Report of January 2002, these authors said:

"*The approach adopted by the group became dominated by the perspective of sufferers* (when did the perspective of sufferers cease to be a legitimate consideration in medicine?) *and, predictably, led to the conclusion that the scale and, in some cases, the severity of the condition, establish its authenticity and dictate the need for NHS provision****…..The group's recognition of CFS/ME as a distinct syndrome runs counter to trends in recent research****….****It is likely that the 'reality' of discrete syndromes such as CFS/ME reflects bias in the referral and selection processes inherent in medical specialisation****…..Patients with persistent unexplained physical symptoms (PUPS) believe themselves to be ill…****The activities of pressure groups are tending to perpetuate discrete syndromes such as CFS/ME…The prevailing view in UK primary care has been that somatisation of mental illness is the basic problem…Approaches which focus on changing the way patients and doctors communicate about the illness and, in particular, incorporate and modify patients' beliefs, are gaining ground****…****A number of authors* (citing Edward Shorter and Elaine Showalter) *have pointed to the primacy of cultural and social factors in creating ill-defined syndromes, suggesting that they are akin to other types of 'social epidemic'…Some individuals…may translate physiological manifestations of unhappiness into symptoms of illness, with* ***the gains involved in adopting victim status****…****The fundamental criticism of the CMO's group is that by adopting an approach that allowed consumerism in health care to define an illness, it surrendered a role reserved for the profession's established scientific methods****…The uncritical diversion of NHS resources…into CFS/ME will not diminish the problem…For****, unless the medical profession clearly understands its role in the management of illness beliefs and behaviour in the absence of demonstrable pathology, it risks becoming an intellectual casualty and a potent vector of this and other social epidemics****"** -- JRCGP 2002:52:478:355-356.

Letters to the Editor in response included one from Hooper et al, who said: *"The authors seem to have fallen into the common trap for the unwary in that they have equated chronic fatigue with the ICD-classified chronic fatigue syndrome (ME), the exact error for which JAMA was forced to issue a correction as long ago as 1990….Far from welcoming the belated public acceptance of what in reality has been officially recognised by the UK Department of Health and the BMA since 1988, the authors seem to resent the CMO's acknowledgement that it is a 'real' disease. They make not a single mention of any of the mounting number of biomarkers of organic pathology which have been documented worldwide in these patients…Could the authors be invited to explain why they ignore all the evidence which is not consistent with their own (psychiatric) model of unexplained physical illness?…Whilst admittedly the authors are writing in a British journal, they do not attempt to explain how their 'social epidemics' of physical symptoms have come to affect hundreds of thousands of people worldwide who manifest exactly the same physical symptoms when such patients do not even speak the same language and the symptoms embrace the major systems of the body, particularly the nervous system (central, autonomic and peripheral), cardiovascular, immune, musculoskeletal and endocrine…Contrary to the assertions of Stanley et al, there are no gains whatever for those with PUPS and their suffering is immense; the reality is that, far from sufferers adopting the role of victim, it is overbearing medical practitioners who victimise these patients. Anyone who relies, as Stanley et al do, on the surmising of a much-criticised American Assistant Professor of English* (Elaine Showalter) *who equates CFS/ME with abduction by aliens as scientific evidence to support their own theories must be at something of a loss in the field of neuroendocrine immunology. In our opinion, Stanley et al have publicly exposed their own biased and limited approach to these problems and their own failure to get to grips with one of the most complex areas of medicine; in this they are not alone, because certain UK psychiatrists whose work is so often funded by charities and trusts linked to commercial interests seem to have the same problem".*

The Wessely School continue to demonstrate an unjustifiable denial of the biomedical evidence showing that ME/CFS is a serious organic disorder akin to HIV/AIDS. Their unremitting intention to eradicate ME and to claim "CFS" as a mental health disorder has chilling implications and serious long-term consequences worldwide for the management of people with ME/CFS.

That there is a concerted campaign by members of the Wessely School to re-classify as a single somatoform disorder various organic syndromes for which a definitive test remains elusive cannot be rationally disputed.

Although only marginally relevant to the MRC PACE Trial, it is worth noting that the British Medical Journal recently carried a well-structured Clinical Review of interstitial cystitis (claimed by Wessely et al as

a functional somatic syndrome), a condition associated with gross bladder wall changes, and painful bladder syndrome, which exhibits the same symptoms but lacks gross cystoscopic findings (Serge Marinkovic et al; BMJ 8th August 2009:339:337-342). The authors stated that patients with IC are 100 times more likely to have irritable bowel syndrome and are 30 times more likely to have systemic lupus erythematosus, and that other associated chronic illnesses include fibromyalgia and chronic fatigue syndrome. The authors provided a compelling but unconfirmed theory – based on evidence that the authors say represents the majority opinion of researchers actively involved in the field – of likely autoimmune causation:

"*The pathological features of bladder epithelial damage and related blood vessel transitions in the absence of infection have been recognised for more than 100 years… One theory is that increased permeability of the protective glycosaminoglycan lining of the bladder epithelium causes potassium (and) toxins to leak into the mucosal interstitium, activating mast cells and generating an autoimmune response. Mast cells produce immune reactive chemicals, which in turn cause generalised bladder inflammation and bladder mucosal damage through the presence of tachykinins and cytokines. These further mediate the release of histamine, tumour necrosis factor, chymase, tryptase, and prostaglandins. Finally, inflammatory agents sensitise bladder neurones, producing pelvic and bladder pain…..Some patients have exacerbations of their symptoms after ingesting certain food or drinks….Urothelial cell cultures express abnormal gene variants. When urothelial biopsies…were subjected to stretch…they released significantly higher concentrations of ATP than control biopsies, suggesting that ATP plays an important role in this syndrome. An investigation of cultured bladder urothelial cells…showed that such cells had higher than normal concentrations of ATP, which decreases the ability of the bladder wall to conduct potassium ions…which again indicates that impaired potassium conduction is involved in the pathophysiology of interstitial cystitis".*

Wessely, however, seemed immediately to reject outright any autoimmune or allergic component: *"The article…details associations with fibromyalgia, chronic fatigue syndrome and, strikingly, a 100-fold increased risk of irritable bowel syndrome – all of which have good evidence for the role, at least in part, of psychological factors in the their aetiology or maintenance…It is highly possible that psychological factors have an aetiological contribution to conditions such as painful bladder syndrome. Such disorders, where physical pathology cannot fully account for symptoms, are known as 'medically unexplained' or 'functional' (somatic) syndromes…It has been proposed* (citing his own Lancet paper 1999:354:936-939) *that they may be the same underlying disorder manifesting itself in different bodily systems…Dr Marinkovic, however, despite drawing out the evidence for such a description, seems to resist the inference, making no mention of psychological factors even as possible contributors to the aetiology…The experience of other functional somatic syndromes…is that a biopsychosocial approach is the foundation of successful cognitive behavioural therapy. This…surely deserves a place in any review (of) painful bladder syndrome"* (http://www.bmj.com/cgi/eletters/339/jul31_2/b2707#218935).

People must decide for themselves whether or not, based on the evidence, Dr Marinkovic did "draw out the evidence" that IC is a functional somatic disorder, and which of the two theories they believe.

Professor Nancy Klimas from the University of Miami has confirmed that interstitial cystitis overlaps with ME/CFS (New York Times, 21st January 2010: http://consults.blogs.nytimes.com/2010/01/21/hiv-fibromyalgia-and-chronic-fatigue-syndrome/).

Based on the evidence, a miniscule amount of which has been included in this Report, people must also decide for themselves whether the Wessely School is correct that ME/CFS is a behavioural disorder that will respond favourably to their cognitive restructuring interventions that are being studied in the MRC PACE Trial.

If considered in conjunction with the illustrations in Section 2, the quotations from the PACE Trial Manuals which follow may help them make up their mind.

SECTION 2: COUNTER-EVIDENCE: THE BIOMEDICAL BASIS OF ME/CFS

This section is included because it is essential to inform readers of the extensive evidence of the biomedical basis of ME/CFS that the MRC PACE Trial Investigators choose to ignore and / or dismiss.

Despite the absence of a definitive test, ME/CFS is clinically recognisable: "*Once one is familiar with the concept of (ME/CFS), such patients are in practice not too difficult to differentiate from those with true psychiatric illnesses…The physical symptoms should be an aid to diagnosis, although they may be wrongly attributed to primary psychiatric illness unless care is taken in eliciting them"* (Professor Rachel Jenkins; BMB 1991:47:4:241-246).

Fifteen years later, Professor Nancy Klimas said: ***"There are diagnostic criteria that enable clinicians to diagnose (ME)CFS in the primary care setting"*** (CDC Press Conference to launch the (ME)CFS Toolkit, November 2006) which enable all conscientious clinicians to feel confident in making the diagnosis.

Although there is as yet no definitive test, there are numerous accredited biomarkers of pathology in ME/CFS (see below), all of which lend support to the diagnosis.

As stated by Dr Suzanne Vernon (see Section 1 above), there are now over 5,000 worldwide peer-reviewed scientific papers (and numerous textbooks) showing that ME/CFS is a complex multi-system disorder involving demonstrable pathology not only of the central and autonomic nervous systems but also of the immune, cardiovascular and endocrine systems, and that on-going inflammation is a significant feature, with damage to skeletal and cardiac muscle as well as to other end organs including the pancreas and liver.

In his presentation at the Royal Society of Medicine meeting on ME and CFS held on 11th July 2009, consultant neurologist Dr Abhijit Chaudhuri demonstrated evidence from three autopsies of people who had died from ME/CFS, **all of which showed inflammatory changes in the dorsal root of the spinal cord. His abstract states that all three autopsies provide "*evidence of neuroinflammation in the dorsal root ganglia, which are the gatekeepers of peripheral sensory information travelling to the brain. This finding may help explain the high level of fatigue and pain*".**

For many years research has shown evidence of enterovirus (Coxsackie B) in the tissues of people with ME/CFS, which was roundly dismissed by Wessely School psychiatrists. More recent work of Douche-Aourik F et al (Journal of Medical Virology 2003:71:540-547) confirmed earlier work: "*Enterovirus RNA has been found previously in specimens of muscle biopsy from patients with…(ME)CFS. These results suggest that skeletal muscle may host persistent enteroviral infection. The presence of viral RNA…is in favour of a persistent infection involving defective viral replication".*

Research has continued to provide evidence of long-term enteroviral persistence in the face of the adaptive immune response: ***"This previously unknown and unsuspected aspect of enterovirus replication provides an explanation for previous reports of enteroviral RNA detected in diseased tissue in the apparent absence of infectious viral particles"*** (Human Enterovirus and Chronic Infectious Disease. Steven Tracy and Nora M Chapman. Journal of IiME 2009: 3:1).

A recent paper reported that biopsy of muscle fibres in ME/CFS showed that fibre-type proportion was *"significantly altered in (ME)CFS samples"* and concluded: ***"Taken together, these results support the view that muscle tissue is directly involved in the pathogenesis of (ME)CFS"*** (Int J Immunopathol Pharmacol 2009:22(2):427-436).

Another recent paper demonstrated that a large percentage (95%) of patients clinically diagnosed with (ME)CFS have elevated levels of the IgM isotope to CL (cardiolipin), suggesting that acute phase lipids may be part of disease pathogenesis in patients with (ME)CFS. These lipids may be analogous to acute phase proteins triggered by cytokines involved in the inflammatory processes in the liver, such as C-reactive

protein and serum amyloid A (which have been reported in ME/CFS and other diseases attributed to toxic chemicals). The authors note that a survey of the literature reports ACAs (anticardiolipin antibodies) as common serological markers in many diseases, including diseases resulting from viruses and chemical exposure, as well as autoimmune diseases such as multiple sclerosis and lupus erythematosus. **The authors conclude that (ME)CFS may be an autoimmune disease**, and that classification of it as such may serve to increase the availability options for patients suffering from the disease. They confirm that experiments are under way to elucidate why ACAs are produced in (ME)CFS, and that these studies are investigating the effects of specific chemical agents on mitochondrial metabolic pathways that are indicative of blocked energy production as occurs in (ME)CFS (Yoshitsugi Hokama et al. J Clin Lab Anal 2009:23:210-212).

Yet more research has shown that (ME)CFS is an autoimmune disorder: Ortega-Hernandez et al looked at the influence of autoantibodies, polymorphisms in the serotonin pathway, and HLA Class II genes in relation to (ME)CFS, and tested autoantibodies to different components of the central nervous system. They conclude: "*Our results reveal that in (ME)CFS, **like other autoimmune diseases**, different genetic features are related to age at onset and symptoms"* (Ann N Y Acad Sci 2009:1173:589-599).

Blaney et al looked at a number of chronic and autoimmune conditions (including multiple sclerosis, lupus, fibromyalgia and (ME)CFS) and demonstrated the use of 1,25-D (1,25-dihydroxyvitamin D3) as a clinical marker in autoimmune conditions, with results that "*showed a strong positive association between these autoimmune conditions and levels of 1,25- D greater than 110 pmol/L"*, noting that high levels of 1,25-D may result when dysregulation of the vitamin D receptor prevents it from expressing enzymes necessary to keep 1,25-D in a normal range (Ann N Y Acad Sci 2009: 1173:384-390).

It has long been known that the resting energy expenditure (REE) in ME/CFS patients is abnormally high (see, for example: J Neurol Sci 1997:150:S225; JCFS 1998:4:4:3-14; Medical Hypotheses 2000:54: (1):59-63). When individual resting energy expenditure (REE) was predicted on the basis of total body potassium values, 45.5% of the (ME)CFS patients tested had resting energy expenditure above the upper limit of normal, suggesting that there is upregulation of the sodium-potassium pump in (ME)CFS. There was no evidence that the results were due to lack of activity (which would have affected total body water estimates).

Given that the energy expended at rest by the ME/CFS patient is significantly elevated when compared with controls, it is not difficult to understand what may be the result when the ME/CFS patient is subjected to even minimal exercise.

ME/CFS is not "medically unexplained"

The seminal work of Martin Pall, Professor Emeritus of Biochemistry and Basic Medical Sciences, Washington State University, is thought to have unravelled the mechanisms that underlie what the Wessely School regard as "functional somatic syndromes", including ME/CFS, fibromyalgia, irritable bowel syndrome and multiple chemical sensitivity (MCS).

Professor Pall's work is quoted with his specific permission (from his paper "Multiple Chemical Sensitivity: Toxicological and Sensitivity Mechanisms" on his new website http://www.thetenthparadigm.org); see also his book "Explaining 'Unexplained Illnesses': Disease Paradigm for Chronic Fatigue Syndrome, Multiple Chemical Sensitivity, Fibromyalgia, Post-Traumatic Stress Disorder, Gulf War Syndrome and Others". Harrington Park (Haworth) Press, New York, 2007 and "The NO/ONOO-Cycle as the Cause of Fibromyalgia and Related Illnesses"; In: New Research in Fibromyalgia, Ed. John A. Pederson, pp 39-61; Nova Science Publishers, Inc 2006.

Pall's ME/CFS Review, a requested paper on ME/CFS in a Nova Biomedical volume on ME/CFS was due to be published towards the end of 2009, and chapter XX in the prestigious toxicology reference book "General and Applied Toxicology", 3rd Edition, Eds. Ballantyne, Marrs and Syversen was published by John Wiley & Sons on 23rd October 2009. The press release for this book says: "*1. MCS is a stunningly common disease, even more common than diabetes. 2. MCS is caused by toxic chemical exposure. 3. The role of chemicals acting as toxicants in MCS has been confirmed by genetic studies. 4. We have a detailed and generally well supported mechanism for MCS. 5.* ***For over 20 years, some have falsely argued that MCS is a psychogenic disease. This view is completely incompatible with all the evidence. It is clear now that MCS is a physiological disease initiated by toxic chemical exposure".***

Given that MCS in the form of intolerance to everyday household chemicals and foods, and to medicinal drugs -- especially those acting on the central nervous system -- is a well-documented feature of ME/CFS (a feature that in May 1994 at the Dublin International Symposium on the disorder held under the auspices of The Ramsay Society and The World Federation of Neurology, the internationally renowned neurologist Professor Charles Poser of Harvard described as pathognomonic of the disorder), Pall's work cannot be separated from the body of knowledge that now exists about ME/CFS.

For a resume of Pall's significant paper "Exquisite Chemical Sensitivity Mechanisms in MCS" (FASEB 2002:16:1407-1417), see http://www.meactionuk.org.uk/Resume_of_Pall_MCS_paper_-_August_2002.htm

Pall provides compelling evidence that none of these overlapping disorders is a somatoform disorder and that the Wessely School paradigm is deeply flawed.

Pall posits that these multi-system chronic disorders are initiated and maintained by chemicals that produce a toxic response in the body, characterised by NMDA activity.

NMDA is N-methyl-D-aspartate, an amino acid derivative acting at the NMDA receptor, mimicking the actions of the neurotransmitter glutamate on that receptor. Glutamate is the most important excitatory transmitter in the brain. Activation of NMDA receptors results in the opening of an ion channel. A unique property of the NMDA receptor is that it allows changes in the flow of sodium, calcium and potassium into and out of the cell.

The main classes of chemicals that initiate multi-system disorders such as ME/CFS are the very large class of organic solvents and related compounds, and three classes of pesticides: (i) organophosphorus and carbamate pesticides, (ii) the organochlorine pesticides and (iii) the pyrethroid pesticides, all of which are known to produce a common toxic response in the body (ie. increased activity of the NMDA receptors).

Increased NMDA activity is known to produce increased calcium influx into cells, leading to increased activity of two calcium-dependent nitric oxide synthases, nNOS and eNOS, which in turn produce increased nitric oxide. Nitric oxide reacts with superoxide to form peroxynitrite, a potent oxidant. Peroxynitrite leads to a partial breakdown of the blood-brain barrier, leading to increased chemical access to the brain. This cycle is known as the NO/ONOO- cycle.

Cases of ME/CFS are also commonly initiated by viral or bacterial infection, including Coxsackie, Epstein-Barr, rubella, varicella, parvovirus, Borna and Ross River viruses; such viral initiating stressors also act to increase nitric oxide levels, which is the common feature. Physical trauma also increases nitric oxide levels.

Once the cycle is initiated, it becomes the cause of the chronic illness, with the initiating chemical, viral or traumatic stressor often long gone.

Pall notes that the most characteristic symptom in ME/CFS is the inability to deal effectively with exercise, and that it has been observed that the difference in ME/CFS patients in response to exercise is

their cortisol response, in that ME/CFS patients' cortisol level fails to rise but stays the same (or even drops) after exercise.

It is known that HPA axis dysfunction occurs not only in ME/CFS but also in other NO/ONOO-cycle diseases including fibromyalgia and multiple chemical sensitivity, as well as in many other chronic inflammatory diseases, so changes in cortisol control are not specific to ME/CFS.

However, **there is published evidence that ME/CFS patients may have a specific change in cortisol regulation** (Demitrack MA, Crofford LJ. Ann N Y Acad Sci 1998:840:684-697; Crofford LJ et al. Brain Behav Immun 2004:18:314-325; Adler GK et al. The Endocrinologist 2002:12:513-522), **indicating that the post-exertional increase in symptoms may be explained by the hypocortisol responses.**

Significantly, Jammes et al reported that markers of oxidative stress increased more in ME/CFS patients after exercise (J Intern Med 2005:257:299-310), a finding that is entirely consistent with a NO/ONOO-cycle elevation.

Pall notes that there is evidence that lowered cortisol levels can produce cardiac dysfunction, a common finding in ME/CFS (http://www.meactionuk.org.uk/Cardiovascular.htm), **and that the need for cortisol may be particularly important during and immediately following exercise due to the stress placed on the heart by exercise, suggesting that the cardiac dysfunction seen in many ME/CFS patients may be caused by their lowered cortisol production during and following exercise.**

For the avoidance of doubt, the MRC PACE Trial Principal Investigators did not consider it necessary to measure participants' cortisol levels; furthermore, Baschetti et al noted that many people diagnosed on the Wessely School's Oxford criteria do not have the hypocortisol response to exercise and therefore may not have true ME/CFS (J Intern Med 2005:258:292-292).

Pall provides evidence supporting each of the following in ME/CFS and related multi-system disorders:

- excessive NMDA activity
- elevated levels of nitric oxide
- elevated peroxynitrite
- oxidative stress
- breakdown of the blood/brain barrier
- inflammatory biochemistry
- elevated levels of inflammatory cytokines
- elevated TRPV1 activity (the vanilloid receptor opens calcium channels, allowing too much calcium into cells, resulting in cellular dysfunction in a whole range of cells, for example, muscle cells contract, causing spasm, and there is increased secretion from secretory cells, ie. it is a multi-system stimulus)
- mitochondrial / energy metabolism dysfunction
- neural sensitisation
- neurogenic inflammation.

The Wessely School's claims that ME/CFS and related multi-system disorders are psychogenic are clearly flawed because none of the psychogenic advocates has considered how chemicals can act as toxicants in the body, yet they have dismissed this model as a "belief" without providing any evidence to support their own beliefs.

As Pall says: ***"Clearly one cannot claim to be doing science whilst simultaneously ignoring most of the relevant scientific literature. Wherever data exists clearly contradicting their views, they simply pretend it does not exist".***

When in 2002 Stanley, Salmon and Peters from the UK wrote an editorial for the British Journal of General Practice (referred to above) arguing that "CFS/ME" is a *"social epidemic"* in which symptoms are generated by psychogenic mechanisms and asserting that these issues *"must be interpreted within a rigorous scientific framework"* (Br J Gen Pract 2002:52:355-356), Pall wrote to the Editor listing eight different objectively measurable physiological changes that had been repeatedly found in ME/CFS patients:

- immune (NK) cell dysfunction
- elevated levels of inflammatory cytokines
- elevated levels of neopterin
- elevated levels of oxidative damage
- orthostatic intolerance
- elevated levels of 37 kD RNase L
- mitochondrial dysfunction
- neuroendocrine dysfunction.

Pall challenged Stanley, Salmon and Peters to show that each of these eight abnormalities was consistent with their interpretation of a *"rigorous scientific framework"*.

Their response was astonishing: they accused Pall of "*a naïve form of reductionism"* and asserted that there was no need for them to question the validity of the physiological findings, as the findings could be *"secondary consequences"* that are *"entirely consistent with the social origins of persistent unexplained physical symptoms (PUPS)"* (Br J Gen Pract 2002:52:763-764).

As Pall notes in his book "Explaining 'Unexplained Illnesses'":

"One of the great puzzles about the psychogenic literature regarding these multisystem illnesses is how do so many bad papers get published? How do so many papers dominated by emotion laden phrases, by transparent falsehoods, by logical flaws, by overstated claims and by unsupported or poorly supported opinion get published in what appear to be respectable, peer-reviewed journals? *These papers consistently ignore massive amounts of contrary data and opinion and cannot, therefore, lay claim to objective assessment of the literature.*

" This is by far the largest failure of the peer-review system that I am aware of. I am almost tempted to call this failure inexplicable.

"I can't help speculate on…the abject failure of the psychogenic advocates to uphold even the minimum of scientific standards".

The Wessely School persistently fail to assess the scientific evidence and continue to base their beliefs on ignorance rather than current knowledge, an ideology that, according to Pall, is intellectually bankrupt.

Mindful that multiple chemical sensitivity is a well-recognised component of ME/CFS for many sufferers, to quote again from Pall's book:

"It is difficult to encompass the damage created by the psychogenic advocates. They have made it difficult to obtain research funding on the physiological basis of these multisystem illnesses. *This difficulty has been particularly profound for MCS, where not coincidentally the fear of massive liability has created major vested interests among industries who have a legitimate fear of law suits that may parallel the liability of the cigarette companies.* ***What is not legitimate is to use their economic and political influence to stifle the scientific and health needs****. And what is not legitimate, is to continue the fiction that MCS is unrelated to chemical exposure, such that millions of additional people inevitably become chemically sensitive due to what should be avoidable chemical*

exposures. ***Responsibility for these millions of additional new cases of MCS should be placed squarely on the door of the psychogenic advocates and their financial supporters.***

"Those who fear illegitimate claims of liability, whether they are insurance companies concerned about disability claims or claims for health benefits or companies using or producing synthetic chemicals, such companies have an obvious route to minimize such claims. They should be using their influence with the media, with political organizations and with scientists to push for research leading to the development of specific biomarkers of these illnesses such that any illegitimate claims can be falsified. ***Their failure to do this is sufficient evidence to infer that these powerful and very canny organizations have a different goal entirely: it is to deny legitimate claims and therefore deny any culpability on their part. To the extent that psychogenic advocates act to encourage such behaviour, they have a lot to answer for. To the extent that they make it difficult to develop truly effective therapies for these illnesses, they have still more".***

For the avoidance of doubt, the American Medical Association 2008 Annual Meeting Highlights for the AMA House of Delegates Reference Committee on Amendments to the Constitution and Bylaws states: "*The AMA will encourage the training of medical students, physicians and other health professionals on the human health effects of toxic chemical exposure*"; clearly -- unlike the Wessely School -- the AMA does not regard MCS as a non-existent disorder (http://www.ama-assn.org/ama1/pub/upload/mm/471/refcomhighlights.pdf).

Despite the Wessely School's perpetual denial, much is now known about ME/CFS

On 18th February **1993**, Professor Paul Cheney from Capital University, USA, testified before the US FDA Scientific Advisory Committee:

"I have evaluated over 2,500 cases. At best, it is a prolonged post-viral syndrome with slow recovery. At worst, it is a nightmare of increasing disability with both physical and neurocognitive components. The worst cases have both an MS-like and an AIDS-like clinical appearance. We have lost five cases in the last six months. The most difficult thing to treat is the severe pain. Half have abnormal MRI scans. 80% have abnormal SPECT scans. 95% have abnormal cognitive-evoked EEG brain maps. Most have abnormal neurological examination. 40% have impaired cutaneous skin test responses to multiple antigens. Most have evidence of T-cell activation. 80% have evidence of an up-regulated 2-5A antiviral pathway. 80% of cases are unable to work or attend school. We admit regularly to hospital with an inability to care for self".

In **1994**, one of the world's most renowned ME/CFS clinicians, Dr Daniel L Peterson from the US, powerfully expressed the severity of 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***" (Introduction to Research and Clinical Conference, Fort Lauderdale, Florida, October 1994; published in JCFS 1995:1:3-4:123-125).

In **1995,** Professor Mark Loveless, Head of the AIDS and ME/CFS Clinic at Oregon Health Sciences University said in his Congressional Briefing that an ME/CFS patient: "***feels effectively the same every day as an AIDS patient feels two weeks before death; the only difference is that the symptoms can go on for never-ending decades***".

In **2004**, Dr William Reeves, Chief of the ME/CFS research programme at the US Centres for Disease Control, (CDC) reported that ME/CFS patients "***are more sick and have greater disability than patients with chronic obstructive lung or cardiac disease, and that psychological factors played no role***" (Press Release, AACFS, 7th October 2004).

Also in **2004**, a randomised clinical trial found "***In comparison with other chronic illnesses such as multiple sclerosis, end-stage renal disease and heart disease, patients with (ME)CFS show markedly higher levels of disability***" (Am J Occup Ther 2004:58:35-43).

In **2005**, Nancy Klimas, Professor of Medicine, Division of Immunology, University of Miami; Co-Director, E.M. Papper Laboratory of Clinical Immunology; Professor of Microbiology and Immunology, University of Miami, and Director of AIDS Research and Co-Director of the AIDS Clinical Research Unit, Miami VA Medical Centre, said in her American Association for CFS In-coming Presidential Address: "***Our patients are terribly ill, misunderstood, and suffer at the hands of a poorly informed medical establishment and society***".

In a Keynote Lecture on 27th May **2007** at the ME Research UK International Conference held at the University of Edinburgh, Nancy Klimas listed the three main categories of diagnostic symptoms as being autonomic, inflammatory and endocrine, all of which indicate serious underlying pathology. Klimas, a world expert in ME/CFS, was one of the authors of "Myalgic Encephalomyelitis / Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols" (JCFS 2003:11(1):7-115), which is usually known as "the Canadian Definition". An Overview of that document ("ME/CFS: A Clinical Case Definition and Guidelines for Medical Practitioners") states:

"*ME/CFS is an acquired organic, pathophysiological, multisystemic illness that occurs in both sporadic and epidemic forms. Myalgic Encephalomyelitis (ICD 10 G93.3), which includes CFS, is classified as a neurological disease in the World Health Organization's International Classification of Diseases (ICD). Chronic fatigue must not be confused with ME/CFS because the "fatigue" of ME/CFS represents pathophysiological exhaustion and is only one of many symptoms. Compelling research evidence of physiological and biochemical abnormalities identifies ME/CFS as a distinct, biological, clinical disorder"* (http://www.cfids-cab.org/MESA/me_overview.pdf).

Long-time clinician and researcher Professor Paul Cheney has stated that 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. Cheney, a world expert on heart problems in ME/CFS, is on record as stating that all patients with the cardinal symptomatology of ME/CFS are in a form of heart failure (http://www.meactionuk.org.uk/Facts_from_Florida.htm). For over 25 years, Cheney has pioneered clinical research into ME/CFS. He has lectured around the world on ME/CFS and is an internationally recognised authority; he has authored or co-authored over 35 articles in peer-reviewed medical journals, including three landmark studies (PNAS 1991; Ann Int Med 1992; Clin Inf Dis 1994); his pre-medical background as a physicist (PhD, Duke University) and as research associate in the Division of Tumour Immunology at the Centres for Disease Control informed his efforts to understand complex medical diseases such as ME/CFS (Cheney Press Release, Co-Cure RES; NOT: 8th October 2009).

A DePaul University (US) study found that patients diagnosed according to the Canadian criteria had more variables that significantly differentiated them statistically from the psychiatric comparison group, and that the Canadian criteria selected cases with less psychiatric co-morbidity and more physical impairment (JCFS 2004:12(1):37-52) but in its Clinical Guideline CG53 on "CFS/ME", NICE recommended that the Canadian Criteria should not be used in the UK.

For Wessely School psychiatrists so persistently to disregard this evidence-base and to assume and assert that those severely affected by ME/CFS are merely somatising is held by many to amount to professional negligence, because the Wessely School's beliefs are contrary to the available biomedical evidence.

In stark contrast to the Wessely School's apparent intellectual dishonesty, in his "Forward" to the book "Lost Voices from a hidden illness" by Natalie Boulton (Invest in ME, 2008), Professor Leonard Jason, Vice-President of the International Association for CFS/ME, wrote:

"*In telling their stories so poignantly, '**Lost Voices' sheds new light on the urgent needs of people who are very ill. It is hard to imagine or understand the shattered world experienced by patients in this book**. Patients with extreme illnesses like ME are often sequestered in their homes (and) there are hundreds of thousands of people who live in this underworld inhabited by a devastating illness. **Even though ME is a debilitating medical condition, many physicians continue to believe that most patients with this disease are suffering from a psychiatric***

illness (and) these biases have infiltrated the media. The traditional healthcare system often refuses to treat people with ME. When treatment is offered, all too frequently social service personnel will refer people with ME to psychiatric services*. The patients of 'Lost Voices' and their carers are heroes in the best sense of the term".*

Fourteen years earlier, in his Eliot Slater Memorial Lecture in May 1994 referred to above, Simon Wessely said: *"Organic diseases lose their credibility as their psychological causes are recognised"*. Despite Wessely's confident assertion, it has not been possible to find an example of an organic disorder losing its organic status when its psychological cause was recognised.

The Wessely School has ensured that virtually no biomedical research has been allowed to challenge their steadfast belief that ME is a primary psychiatric disorder, and the result is the harrowing human suffering revealed in 'Lost Voices'.

Wessely did not mention that psychiatrists have a long track record of medical misattribution: the literature is replete with examples of diseases with (then) "unexplained" symptoms that psychiatrists claimed – with absolute certainty – as psychosomatic. These diseases include diabetes mellitus; epilepsy; multiple sclerosis, Graves' disease; pernicious anaemia; myasthenia gravis; Parkinson's Disease; gastric ulcer; migraine; Dupuytren's contracture; gout; glaucoma; asthma; angina; ulcerative colitis and hay fever (Case Histories in Psychosomatic Medicine. Miles HHW, Cobb S and Shands HC (eds); 1959; WW Norton & Co Inc., New York).

As noted by George Davey-Smith, Professor of Clinical Epidemiology at Bristol, a further example is that in 1948 – long before H-Pylori was discovered in 1989-- doctors in Mount Sinai Hospital advocated antibiotics for peptic ulcers, a treatment they knew was successful. A patent for an antibiotic formulation was issued in 1961, but the "stress model" served to block people from building on this and moving towards an answer that would have led to a treatment that could have dramatically improved the quality of life for millions of people. Various psychological interventions for peptic ulcer were advocated and large numbers of people were subjected to them. The usual claims for dramatic success were made, but properly conducted randomised controlled trials demonstrated no benefit. The conclusion of one well-conducted trial was that "*our study demonstrates a need for humility about the degree to which psychological interventions can effect powerful biological processes".* Sick people were directed away from a treatment for peptic ulcers that really worked – antibiotics – to ones that did not work, and the answer that could have led to an effective treatment was missed because of a particular model --- essentially the BPS (biopsychosocial) model --- and the mindset that it generated (Biopsychosocial Medicine, OUP 2005; ed. Peter White).

Davey-Smith is the one dissenting voice in Biopsychosocial Medicine: his contribution ("The biopsychosocial approach: a note of caution") carries the torch for intellectual integrity.

Davey-Smith showed that bias can generate spurious findings and that when interventional studies to examine the efficacy of a psychosocial approach have been used, the results have been disappointing. To quote from Davey Smith's contribution: "*Over the past 50 years many psychosocial factors have been proposed and accepted as important aetiological agents for particular diseases and then they have quietly been dropped from consideration and discussion*". The illustrations he cited included cholera, pellagra, asthma and peptic ulcer.

Davey-Smith went on to quote Susan Sontag's well-known dictum: "*Theories that diseases are caused by mental state and can be cured by willpower are always an index of how much is not understood about the physical basis of the disease*" (Illness as a metaphor. Random House; New York. 1978).

In his book "The Greatest Benefit to Mankind" (Harper Collins, London, 1997) the late Roy Porter noted that it was the biomedical model (not the psychosocial model) that has provided advances in the understanding -- and thus in the treatment and prevention -- of disease processes.

Evidence that the PACE Trial Investigators chose to ignore

In **1996**, US neurologist Dr Benjamin Natelson et al evaluated patients with ME/CFS for a placebo effect in a randomised, double blind, controlled trial and found no evidence that ME/CFS is an illness due to patients being overly suggestible or that ME/CFS is a psychogenic illness, and that: *"**No clear effect of any treatment has ever been demonstrated in this devastating illness**"* (Psychopharmacology 1996:124:226-230).

In **1996**, Natelson et al examined the rates of somatisation disorder (SD) in ME/CFS relative to other fatiguing illnesses and found that the diagnosis of SD is extremely problematic in terms of its validity because it involves a series of judgments that can be arbitrary and subjective: *"(ME)CFS can be viewed as an organic disease involving many organ systems or as an undifferentiated somatoform disorder. **A diagnosis of somatoform disorder may be so arbitrary as to be rendered meaningless in illnesses such as (ME)CFS**"* (Psychosom Med 1996:58(1):50-57).

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).

Also 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).

Another key paper in **1999** was by Hill, Tiersky, Natelson et al. This study showed that the prognosis for recovery was extremely poor for the severely affected: the majority showed no symptom improvement and only 4% of the patients recovered: *"Not only do patients with severe (ME)CFS not recover to full health, but they remain quite severely ill over many years. **These data suggest that in patients who do not have psychiatric***

diagnoses before (ME)CFS onset, depressed mood is a correlate of illness rather than a risk factor for poor prognosis*. The cost of (ME)CFS is great, both to the individual and to our society"* (Arch Phys Med Rehabil 1999:80:1090-1094).

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 response to an article in the BMJ 2002:324:1298 that promoted CBT and GET as the only effective treatments for "CFS/ME", on 9th June 2002 the following was published in the eBMJ:

"More naïve research: As a long-term CFS sufferer and retired psychology lecturer who taught CBT and behaviour modification, I can confirm that I have tried CBT and graded exercise and it does not work. CBT cannot do anything for the underlying physical and neurological problems. Hence CBT is a red herring for most of us long-term sufferers. What we need is serious research into the underlying factors" (James Wolsey).

In **2003**, US researchers Tiersky and Natelson et al showed that in patients with ME/CFS, co-morbid psychiatric disorder, including anxiety or depression, is not related to physical disability in those who developed psychiatric disorder after becoming ill, in contrast to other diseases wherein co-morbid psychiatric disease does compromise physical functioning. Tiersky et al found that people with ME/CFS suffer from profound physical impairment, with scores below the standard norm for patients with type II diabetes, arthritis, cancer, congestive heart failure, hypertension and myocardial infarction (J Nerv Ment Dis 2003:191:324-331).

Natelson was also part of the research team that found left ventricular failure upon exertion in a subset of ME/CFS patients, which again produced hard scientific data using sophisticated tests that showed the profound disability in this disease. This study argues against the claims by Wessely School psychiatrists that the profound disability of ME/CFS is "*in the cognition of those affected"*.

In **2004**, a US Centres for Disease Control (CDC) Surveillance study found that (ME)CFS subjects did not demonstrate any unique patterns of psychiatric disorders and noted that the CDC places ME/CFS at the top priority of new and re-emerging infectious diseases (EK Axe et al. JCFS 2004:12 (3)).

In **2005**, US researchers Song and Jason investigated whether the psychogenic (behavioural) model of ME/CFS by Vercoulen et al (which characterises patients as having insufficient motivation for physical activity or recovery, lacking self-control, and maintaining a self-defeating preoccupation with symptoms) could be replicated in a community-based sample. The authors noted that for some, ME/CFS was assumed to be a psychologically-determined problem (quoting Wessely and Sharpe), and that while this model has been cited frequently, no critical reviews or replication of the Vercoulen et al study of 1998 (which characterised individuals with ME/CFS as inclined to improperly associate physical activity with a worsening of symptoms) have been published. Song and Jason tested the Vercoulen model six times. The results showed that the Vercoulen model represented those with chronic fatigue secondary to psychiatric conditions, but did not represent those with ME/CFS: *"In other words, the present study does not support a psychogenic explanation for (ME)CFS"* (Journal of Mental Health 2005:14 (3):277-289).

In **2005**, Canadian psychiatrist Eleanor Stein (whose practice specialises in ME/CFS) published "Chronic Fatigue Syndrome: Assessment and Treatment of Patients with ME/CFS: Clinical Guidelines for Psychiatrists" (www.mefmaction.net). **Stein was clear that the Oxford criteria (created and used by the Wessely School) 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**. ME/CFS is not a primary psychiatric disorder; rates of psychiatric disorder in ME/CFS are similar to rates in other chronic medical disorders and studies that reported higher prevalence rates of psychiatric disorder had sampling biases; rates of personality disorder in ME/CFS are not elevated, and illness severity, not psychological factors, predict outcome. 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.*** *Grief is a universal issue for people with ME/CFS. The losses are numerous. Patients with ME/CFS cannot manage ordinary stressors.* ***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.*** *It is likely that activity avoidance is necessary for the severely ill.* ***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".***

In **2006**, Demitrack encapsulated the problem that the Wessely School, NICE and the MRC decline to address. In his paper "Clinical methodology and its implications for the study of therapeutic interventions for chronic fatigue syndrome: a commentary", Demitrack was concise: "*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 entanglement of physical symptoms and behavioural symptoms, and 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.*** *A major consideration in the approach to clinical therapeutics in (ME)CFS is the fact that it is, by definition, a chronic illness. The magnitude of disease chronicity is a feature that has an important impact on overall treatment responsiveness.* ***Given these observations, it is notable that the specific methodology used to measure treatment outcome rarely comes under close scrutiny in studies of therapeutic intervention in this condition. I believe it is crucial that the quality and interpretability of past and future therapeutic studies of (ME)CFS be critically appraised to the extent that they have considered the impact of these issues in their design and conclusions"****.*

Demitrack noted the growing body of central nervous system (CNS) research, especially neuroendrocrine physiology and neuroimaging studies, that have reinforced the view that symptoms may indeed be manifestations of a primary disruption in CNS function. In relation to interventions, Demitrack was unambiguous: "***To appropriately design and implement (successful interventions), it becomes critically important to specify the patient population most likely to benefit from the proposed intervention, and exceedingly important to define the specific symptom, or cluster of symptoms, that may be presumed to benefit from the intervention. In the absence of a coherent understanding of disease pathogenesis, it does not seem plausible that any single intervention would be helpful in an undifferentiated majority of patients. It therefore may not be surprising that current treatment options for (ME)CFS appear only modestly effective. Non-response, or partial response is the norm, and more than half of all patients fail to receive any benefit from many interventions****".*

Demitrack concluded**: *"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).

In **2006**, Jason et al sought to subgroup patients with CFS based on a battery of basic laboratory tests and identified infectious, inflammatory and other subgroups. When compared with controls, all subgroups reported greater physical disability:

"*CFS can impact any number of bodily systems including neurological, immunological, hormonal, gastrointestinal and musculoskeletal. Researchers have reported various biological abnormalities, including hormonal, immune activation, neuroendocrine changes and neurological abnormalities, among others. However, studies involving basic blood work appear to show no typical pattern of abnormality among individuals with CFS.*

"Borish et al (1998) found evidence of low level inflammation, similar to that of allergies. Natelson et al (1993) found that those with ongoing inflammatory processes reported greater cognitive and mental disabilities. Buchwald et al (1997) found individuals with CFS to have significant abnormalities in C-reactive protein (an indicator of acute inflammation) and neopterin (an indicator of immune system activation, malignant disease, and viral infections). Buchwald et al (1997) stated that individuals with active low level inflammatory, infectious processes could be identified and that this was evidence of an organic process in these patients with CFS. Cook et al (2001) found that individuals with an abnormal MRI and ongoing inflammatory processes had increased physical disability, suggesting an organic basis for CFS.

"Clearly, individuals diagnosed with CFS are heterogeneous.

*"**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 *(DeLuca et al. 1997; Hickie et al. 1995; Jason et al. 2001).*

"The relationship between psychiatric diagnosis and CFS diagnosis is one that is far from being understood"*.*

Discussing the subtypes found, Jason et al state: "***It is notable that these findings emerged utilising only a basic battery of laboratory screening tests. Many people with CFS exhibit only minimal or subtle abnormalities on these tests, and these abnormalities may not be acknowledged by the primary care physician.***

"The more commonly reported physiological abnormalities in people with CFS, such as the presence of RNase L (Suhadolnik et al 1997), adrenal insufficiency with subsequent low cortisol levels (Addington 2000), the presence of orthostatic intolerance (Schondorf et al 1999), and immunological abnormalities (Patarca-Montero et al 2000) can only be assessed using highly specialised tests to which people with CFS typically have little access.

"This study demonstrates that subgrouping is possible using laboratory tests that are readily available and can easily be ordered by primary care physicians.

"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).

In **2007** an important article by Jason and Richman reviewed two aspects of ME/CFS: the issues involving the inappropriate name of the illness favoured by some psychiatrists ("chronic fatigue syndrome", which undoubtedly trivialises the disorder), and the flawed epidemiological approaches, both of which may have contributed to the diagnostic scepticism and the stigma that those with ME/CFS encounter.

The authors suggest that the increases in cases during the past 15 years are due to a broadening of the case definition to include those with primary psychiatric conditions (as the Wessely School have done). The authors note how flawed epidemiology can contribute to inappropriate stereotypes, and stress the need for accurate measurement and classification in disorders that might be labelled as 'functional somatic syndromes' (as the Wessely School deems ME/CFS to be).

The authors state: "*Accurate measurement and classification of (ME)CFS, fibromyalgia and irritable bowel syndrome is imperative when evaluating the diagnostic validity of controversial disease entities alternatively labelled 'functional somatic syndromes'.* ***Measurement that fails to capture the unique characteristics of these illnesses might inaccurately conclude that only distress and unwellness characterise these illnesses, thus inappropriately supporting a unitary hypothetical construct called functional somatic syndromes****"* (JCFS 2007:14(4):85-103).

<u>Documented pathology seen in ME/CFS that contra-indicates the use of GET</u>

There is an extensive literature **from 1956 to date** on the significant pathology that has been repeatedly demonstrated in ME/CFS, but not in "CFS/ME" or "chronic fatigue"; this can be accessed on the ME Research UK website at http://www.meresearch.org.uk/information/researchdbase/index.html and also at http://www.meactionuk.org.uk/Organic_evidence_for_Gibson.htm .

According to Professor Nancy Klimas, ME/CFS can be as severe as congestive heart failure and the most important symptom of all is post-exertional relapse (presentation at the ME Research UK International Conference held in Cambridge in May 2008).

Unique vascular abnormalities have been demonstrated in ME/CFS, with markers of oxidative stress. Oxidative stress is caused by highly reactive molecules known as free radicals circulating in the bloodstream and results in cell injury. Oxidative stress levels are significantly raised in ME/CFS and are associated with clinical symptoms. (Kennedy G, Spence VA, McLaren M, Hill A, Underwood C, Belch JJF. Free Radical Bio Med. 2005;39:584-589).

Exercising muscle is a prime contender for excessive free radical generation (Niess AM, Simon P. Front Biosci. 2007 Sep 1;12:4826-38).

Research has shown that many patients with ME/CFS may have an inflammatory condition and be in a 'pro-oxidant' state (Klimas NG, Koneru AO. Curr Rheumatol Rep. 2007;9(6):482-7).

In **1983**, UK researchers documented evidence of a consistent pattern of complexity, including "*malaise, **exhaustion on physical or mental effort**, chest pain, palpitations, tachycardia, polyarthralgia, muscle pains, back pain, true vertigo, dizziness, tinnitus, nausea, diarrhoea, abdominal cramps, epigastric pain, headaches, paraesthesia and dysuria*" (Keighley and Bell, JRCP: 1983:339-341).

Documented muscle abnormalities in ME/CFS

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 post-viral fatigue syndrome, also known as ME, has been recognised recently as a distinct neurological entity with increasing evidence of the organic nature of the disease. 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**, 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).

It was documented as long ago as **1988** that 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).

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*" (JRSM 1988:81:325-331).

Also 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**, as mentioned above, a UK researcher pointed out the folly of CBT/GET: *"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" (Wessely S, David A et al. JRCGP 1989:39:26-29).* ***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****" (D O Ho-Yen JRCGP 1990:40:37-39).*

Also 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 fairly 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"*** (A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpes Type 6 infection. 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****. A few patients have more dramatic neurologic events such as seizures, periods of severe visual impairment, and periods of paresis. Evidence suggests that several latent viruses may be actively replicating more often in (ME)CFS patients that 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"****.*

On 18th February **1993**, Professor Paul Cheney testified before the US FDA Scientific Advisory Committee as follows: *"I have evaluated over 2,500 cases. At best, it is a prolonged post-viral syndrome with slow recovery. At worst, it is a nightmare of increasing disability with both physical and neurocognitive components. The worst cases have both an MS-like and an AIDS-like clinical appearance. We have lost five cases in the last six months.* ***The most difficult thing to treat is the severe pain. Half have abnormal MRI scans. 80% have abnormal SPECT scans.***

95% have abnormal cognitive-evoked EEG brain maps. Most have abnormal neurological examination. *40% have impaired cutaneous skin test responses to multiple antigens. Most have evidence of T-cell activation. 80% have evidence of an up-regulated 2-5A antiviral pathway.* ***80% of cases are unable to work or attend school. We admit regularly to hospital with an inability to care for self"****.*

Also 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 the 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. The presence of the enteroviral sequences in a significant number of patients points to some role in ME/CFS. A variety of immunological disturbances have been reported for ME/CFS patients which may relate in some way to the enteroviral persistence. 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 **1997,** Charles Lapp, Professor of Community Medicine at Duke University, Charlotte, North Carolina, found that a trial allowing ME/CFS patients to reach their maximum oxygen consumption within 8-10 minutes of exercise caused 74% to experience a worsening of fatigue and that none improved. The average relapse lasted 8.82 days. Lapp concluded: "*These findings suggest that, pushed to maximal exertion, patients with ME/CFS may relapse"* (Am J Med 1997:103:83-84).

In **1998,** a study of autonomic function by Rowe and Calkins found that "*Virtually all ME/CFS patients (regardless of their haemodynamic response) have their symptoms provoked by standing upright"* (Am J Med 1998:105: (3A):15S – 21S).

That same year, (**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 that one of these patients had 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 sports medicine and 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 that is seen in ME/CFS. (This presentation was singled out as being outstanding).

The "Exercise Workshop" at this same conference highlighted the understanding that people with ME/CFS suffer exercise intolerance and post-exertional malaise unless they stay within prescribed limits, the limit suggested being the anaerobic threshold (AT -- this is the time during exertion that the heart and lungs can no longer provide adequate oxygen to muscles, and muscle metabolism changes from aerobic to anaerobic; it is well known that this change occurs unusually early in people with ME/CFS). If the anaerobic threshold is determined to occur at 4.5 minutes, then the patient is advised to exert no more than 4 to 4.5 minutes before stopping to rest.

(For conference reports, see http://tinyurl.com/ylzwbmw by Professor Charles Lapp from the US and Co-Cure NOT, RES: 2nd November 2004 by Dr Rosamund Vallings from New Zealand).

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: "*A few years ago, little was known about the nature of chronic musculoskeletal pain in ME/CFS. Research data gathered around the world enables clinicians to understand, at least in part, musculoskeletal pain in ME/CFS patients. Fear of movement (kinesiophobia) is not related to exercise performance in ME/CFS patients. From a pathophysiologic perspective, the evidence of a high prevalence of opportunistic infections is consistent with the numerous reports of deregulated and suppressed immune functioning in ME/CFS patients. Infection triggers the release of the pro-inflammatory cytokine interleukin-1β 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. Although published after the production of the NICE Guideline, the paper contains relevant references showing adverse effects of GET that were published before the Guideline (and so were available to the GDG and also to the PACE Trial Principal Investigators):

"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. CBT represents a psychological and physical intervention approach aimed at assisting individuals in re-evaluating concepts related to their illness and in adopting thoughts and behaviours designed to promote recovery*** (the reference for this statement is Chalder, Deale and Wessely et al. Am J Med 1995:98:419-420). ***This approach to GET advises patients to continue exercising at the same level even when they develop symptoms in response to exercise*** (two references are provided for this statement, one being Fulcher KY and White PD, BMJ 1997:314:1647-1652 – this being one of the RCTs based on the Oxford criteria that the GDG relied upon for its recommendation of GET. The other reference was Clark LV and White PD (J Mental Health 2005: 14: 237-252), in which Clark and White state that patients with ME/CFS are de-conditioned, and argue that: *"Patient education is necessary to inform patients of the positive benefit / risk ratio in order to improve acceptance and adherence"*). Nijs et al continue: "***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*** (ref: Black CD, O'Connor, McCully K. Dynamic Medicine 2005:4:3). ***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; the authors stated that PBC is characterised in 95% of patients by autoantibody responses directed against the mitochondrial antigen pyruvate dehydrogenase complex (PDC). To define mitochondrial function in peripheral muscle during exercise, (31)P magnetic resonance spectroscopy was used.

Whilst the paper is chiefly concerned with mitochondrial dysfunction in patients with primary biliary cirrhosis (and the results clearly indicate mitochondrial dysfunction in patients with PBC, who showed excess muscle acidosis at higher levels of exercise), 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, which is the largest autonomic function testing laboratory in Europe; her work focuses on the role of the autonomic nervous system in the development of fatigue, specifically in primary biliary cirrhosis, but also in the pathogenesis of fatigue in ME/CFS. 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, (ME)CFS and (FM)CFS 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 (ME)CFS patients after exercise suggest that such alterations could be used as objective biomarkers, with ~ 90% of the (ME)CFS patients being distinguishable from controls using four of the genes measured. The authors have shown that 25 minutes of moderate exercise generates large and rapid increases in gene expression in leucocytes of (ME)CFS subjects but not in control

subjects, findings which confirm previous suggestions that alterations in all parts of the HPA axis may mediate and sustain symptoms of (ME)CFS (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).

There is a significant literature suggestive of mitochondrial defects (both structural and functional) in ME/CFS from 1984 to date.

Mitochondria are the powerhouses of the cells. They are responsible for generating energy as adenosine triphosphate (ATP) and are involved in the apoptosis signalling pathway (apoptosis being programmed cell death).

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***". It is notable that the alleged evidence-base upon which the Guideline Development Group relied specifically states: ***"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*".

Medications documented to induce mitochondrial damage include analgesics; anti-inflammatories; anaesthetics; angina medications; antibiotics; antidepressants; anxiolytics; barbiturates; cholesterol-lowering medications (statins); chemotherapy; and the mood-stabiliser lithium, amongst others, including medications for Parkinson's Disease, diabetes, cancer and HIV/AIDS (Mol Nutr Food Res 2008:52:780-788).

It is a matter of record that Professor Wessely advises the prescription of lithium for patients with ME/CFS: "*There is no doubt that at least half of CFS patients have a disorder of mood. The management of affective disorders is an essential part of the treatment of CFS/ME. Numerous trials attest to the efficacy of tricyclic antidepressants in the treatment of fatigue states.* ***Patients who fail to respond should be treated along similar lines to those***

proposed for treatment-resistant depression. Adding a second antidepressant agent, especially lithium, may be beneficial" (The chronic fatigue syndrome – myalgic encephalomyelitis or postviral fatigue. S Wessely PK Thomas. In: Recent Advances in Clinical Neurology (ed): Christopher Kennard. Churchill Livingstone 1990: pp 85-131).

In addition to lithium, specific medications listed that are known to induce mitochondrial damage include aspirin; acetaminophen (paracetamol / Tylenol); fenoprofen (Nalfon); indomethacin (Indocin, Indocid); naproxen (Naprosyn); lidocaine; amiodarone (Cordarone); tetracycline; amitriptyline; citalopram (Cipramil); fluoxetine (Prozac); chlorpromazine (Largactil); diazepam (Valium); galantamine (Reminyl) and the statins, amongst others.

For the Wessely School to subject patients with ME/CFS to graded exercise that will almost certainly induce more pain and thus give rise to ingestion of analgesics that are known to induce further mitochondrial damage cannot be said to be acting in patients' best interests.

Documented cardiovascular abnormalities in ME/CFS

Illustrations of cardiovascular dysfunction in ME/CFS include the following:

1957

One of the most useful and important descriptions of ME is that of Dr Andrew Wallis as contained in his doctoral thesis (An Investigation into an Unusual Disease seen in Epidemic and Sporadic Form in a General Practice in Cumberland in 1955 and subsequent years. Andrew Lachlan Wallis. Doctoral Thesis, University of Edinburgh, 1957). For a summary, see http://www.meactionuk.org.uk/Vade_MEcum.htm .

Wallis particularly noted **myocarditis (heart rate was accelerated during the illness), with dyspnoea on slightest exertion.** The post-mortem histopathology report from one (female) case stated:

"There are in the entire diencephalon, particularly round the third ventricle, numerous small haemorrhages, which extend into the adjacent parts of the mid-brain. Similar haemorrhages can be seen in the corpora mamillare. The haemorrhages are mostly around the small vessels but some are also to be seen in the free tissue. This is a significant finding."

Comparison of the Wallis findings with other published findings

The post-mortem histopathology report in Wallis' thesis was particularly interesting, given the subsequent documented evidence of vascular abnormalities and impaired blood flow in ME/CFS. For example, references in one textbook of ME/CFS to vasculopathy include the following:

"lymphocytes in the cerebrospinal fluid congregate in the perivascular (Virchow Robin) spaces of the brain…these findings do suggest that the disease may involve the perivascular spaces of the brain

*"dilatation of the Virchow Robin spaces could also suggest intracranial arterial or periarterial pathology, in particular, one would expect to find a congregation of lymphocytes in the perivascular spaces around the central nervous system arteries**…(Wallis) revealed an artefact that is in an anatomical position similar to that suggested by MRI studies***

re: the Los Angeles 1934 epidemic: "***The blood vessels throughout the nervous system were distended with red blood cells…the most characteristic change was infiltration of the blood vessel walls***" (The present consensus on MRI in ME/CFS. Royce J Biddle. In: The Clinical and Scientific Basis of ME/CFS. ed: BM

Hyde; The Nightingale Press, Ottawa, Canada 1992). Other references to vasculopathy in ME/CFS in the same textbook include:

page 42 (Chapter 5 / BM Hyde): *"We routinely observe patients with severely cold extremities and a visible line demarcating the cold from the area of normal skin temperature. The fact that the loss of normal blood flow may be persistent has been indicated by Gilliam* (1938)"

page 62: *"Patients will complain of severe blanching of their extremities, nose, ears, lower arms and hands as well as lower legs and feet. Observation will often reveal a blanched clearly demarcated line separating warm from icy cold tissue. The whitened extremities may persist for hours and can be extremely painful"*

page 70: "***The haemorrhages are mostly around small vessels, but some are also to be seen in the free tissue***"

page 73: Hyde discusses the occurrence of Raynaud's Disease in ME/CFS: "*This is common in ME/CFS. These acute Raynaud's Disease changes are visible"*

page 89 (Chapter 8 / John Richardson): *"**A liver biopsy showed a vasculitis of the liver***"

page 91: *"Liver Function Tests are sometimes abnormal and signify a vasculitis of the liver"*

page 250 (Chapter 23 / Jay Goldstein): *"SPECT scanning may justify vasodilator therapy with calcium channel blockers"*

page 286 (Chapter 28 / EG Dowsett): *"ME is a multisystem syndrome including nervous, cardiovascular, endocrine and other involvement. Symptoms and Signs (table 2): Vasculitic skin lesions, autonomic dysfunction, especially circulation and thermoregulation"*

page 376: (Chapter 42: Hyde and Jain: Cardiac and Cardiovascular Aspects of ME/CFS): reference is made to *"frequent vasomotor abnormalities"*

page 377: *"vasomotor disturbances were almost constant findings, with coldness and cyanosis. It was the impression of most observers that a generalised disturbance of vasomotor control occurred in these patients"*

page 377: "*Findings included sinus tachycardia, abnormal T waves in two or more leads (and) prolongation of Q-T interval"*

page 377: "*Myocarditis in the acute phase: the heart rate was accelerated (and) tachycardia was considered to be a diagnostic feature. In four cases there was a persistent rise in blood pressure (which) slowly lowered over a period of many months"*

page 378: *"Cardiovascular symptoms: angina-like pain; vascular headache; orthostatic hypertension; oedema; dyspnoea; transient hypertension"* (note that on page 42, Hyde states about blood pressure regulation: "***Some seem to be unable to adjust blood pressure with body activity, resulting in high blood pressure on modest activity and very low pressure when reclining***")

page 378: referring to Professor Peter Behan's CIBA lecture in 1988: "*using SPECT scan techniques,* ***his team was regularly able to demonstrate micro-capillary perfusion defects in the cardiac muscle of ME patients"***

page 380: ***"These chronic ME/CFS patients complain of severe chest pain and shortness of breath as if suddenly stopped by an invisible barrier"***

page 381: *"Arrhythmias are frequently noted in the first few weeks of illness, then decrease in frequency, only to return in a chronic form 20 years later"*

page 433 (Chapter 49 / Ismael Mena): referring to the need for SPECT scans in ME/CFS patients, Mena states: ***"The accuracy and reproducibility of these measurements are justification to evaluate cerebral perfusion abnormalities in patients with ME/CFS. Most probably, temporal lobe perfusion defects may fingerprint primary inflammatory changes or secondary vascular impairment in these patients"***

page 437: *"the diminished uptake of this oxime can be interpreted as due to a) diminished rCBF* (regional cerebral blood flow)*, b) inflammatory regional changes (present in 71% of patients studied)"*

page 598 (Chapter 65 / LO Simpson): *"if the stasis did not resolve, focal lesions of ischaemic necrosis would develop"*

page 673 (Chapter 75 / J Russell): Dr Jon Russell is a world expert on fibromyalgia (which may be a comorbidity with ME/CFS: *"Fibromyalgia appears to represent an additional burden of suffering amongst those with ME/CFS"*. Buchwald D et al. Rheum Dis Clin N Am 1996:22:2:219-243) and says about the prevalence of vasculitis*: "It is apparent that some patients with fibromyalgia also exhibit vasculitis with a frequency that has caught the attention of clinicians"*.

Since its publication in 1992, this major medical textbook on ME/CFS has been resolutely ignored by the Wessely School and by those Government agencies which they advise.

Other references in the literature to cardiovascular problems in ME/CFS

1976

From the earliest reports of ME/CFS, autonomic vasomotor instability has been noted (AM Ramsay, Update: September 1976:539-541).

1984

There have been many reports of impaired blood flow in the microcirculation (LO Simpson, NZMJ:1984:698-699).

1988

"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" (Behan P. Crit Rev Neurobiol 1988:4:2:157-178).

1989

*"The data are compatible with latent viral effects on cardiac pacemaker cells, or their autonomic control, and skeletal muscle, that are unmasked by the stress of exercise***"** (Montague TJ et al. Chest 1989:95:779-784).

1989

"Persistent viral infections impair the specialised functions of cells. ***Evidence of persistent enterovirus infection has been found in both dilated cardiomyopathy and in myalgic encephalomyelitis****. Immunological and metabolic disturbances in ME may result from chronic infection, usually with enteroviruses, providing the organic*

basis of the postviral fatigue syndrome. This condition is characterised by recuperation through rest. The myocardium, however, cannot rest – except terminally" (NR Grist. BMJ 1989:299:1219).

1990

"A significant group have cardiac symptoms" (Professor Peter Behan, Cambridge Conference Report, 17th March 1990; ME Association Medical Update 1990: 2).

1990

"There is a high incidence of cardiomyopathy in CFS patients" (Dr Jay Goldstein, Director of the CFS Institutes, Anaheim Hills; member of the Faculty of the Department of Psychiatry, University of California; CFIDS Reporter, Oregon, October 1990).

1991

"The patient with Post-viral fatigue syndrome (ME) is referred to a cardiologist almost always because of chest pain. In viral pericarditis, as with ME, there is now abundant evidence that the disease process arises from an abnormal response to a viral infection. *Chest pain is variable in character. It is sometimes severe, sharp and stabbing, or it may be dull and aching. It is unrelated to exertion, although the patient frequently feels the pain to be worse after a day of increased physical activity.* ***The pain may last for several hours or even days.*** *It frequently occurs centrally but even in the same patient may recur on a different occasion in the right or left chest or the back. It is commonly aggravated by sudden movement, change of posture, respiration or swallowing.* ***Palpitations are frequent, with sinus tachycardia being a common and troublesome symptom.*** *The diagnosis of the cause of chest pain in ME rests almost entirely on careful clinical evaluation.* ***Pericarditis may continue or recur for many years and, like ME, be a distressing and debilitating illness****. There is alas no way of predicting how long the condition will persist, and no reliably successful means of treating it"* (Post-viral Fatigue Syndrome and the Cardiologist. RG Gold. In: Post-Viral Fatigue Syndrome. Ed: Rachel Jenkins and James Mowbray. John Wiley & Sons, 1991).

1993

Evidence of repetitively negative to flat T waves on 24-hour ECG monitoring was found in some ME/CFS patients (Lerner AM et al. Chest 1993:104:1417-1421).

1994

Abnormal left ventricular dynamics (i.e. an abnormal pumping mechanism) were demonstrated in ME/CFS patients, including abnormal wall motion at rest; dilatation of the left ventricle, and segmental wall motion abnormalities (Dworkin HJ, Lerner AM et al. Clinical Nuclear Medicine 1994:19:8:675-677).

1994

"As with any chronic inflammatory condition affecting the central nervous system, the T2-bright foci on MR **(**magnetic resonance) ***in ME/CFS may represent perivascular cellular infiltrate and / or reactive demyelination of the surrounding white matter….these abnormalities may reflect the result of a vasculopathy specifically involving the small vessels of the cerebral white matter****; indeed, the distribution of lesions on MR in ME/CFS is similar to that observed in occlusive arteriolar disease of any origin.* ***The cortical defects measured with SPECT may result from decreased flow through cortical arterioles owing to vasculitis. Specifically, on the basis of our observations, the white matter abnormalities seen on MR images may represent chronic demyelination, which appears to be irreversible****"* (Detection of Intracranial Abnormalities in Patients with Chronic Fatigue Syndrome: comparison of MR imaging and SPECT. Schwartz RB, Komaroff AL et al. Am J Roentgenol 1994:162:935-941).

1995

"The use of cardiopulmonary exercise testing is not only valid and reliable, but also serves as an objective indicator for assessing disability. Maximal cardiopulmonary exercise testing provides two objective markers of functional capacity. The first is maximal oxygen consumption. The most important determinant of functional capacity is not maximal oxygen consumption, but anaerobic threshold. ***Typically ME/CFS patients achieve less than 80% of predicted maximal oxygen consumption with an anaerobic threshold lower than 40% of predicted peak oxygen consumption levels.*** *In ME/CFS patients, we have not found re-conditioning to be possible.* ***In fact, attempts to re-condition patients consistently results in exacerbation of symptomatology.*** *Cardiopulmonary exercise testing can be used to provide ME/CFS patients with another objective marker that will aid them in obtaining disability status"* (SR Steven. JCFS 1995:1:3-4:127-129).

1996

At the State of Massachusetts educational workshop given by Professor Paul Cheney, evidence was presented of the complexity of ME/CFS (referred to as "CFIDS", or Chronic Fatigue and Immune Dysfunction Syndrome). According to Cheney, 80% of ME/CFS patients display medication and environmental sensitivities; there is evidence of lymphatic involvement, with the thoracic duct being tender, and the swollen areas on the neck or upper chest being a back-up of lymphatic fluid.

Cheney biopsied 16 digits of people with ME/CFS and found a vasculitis not uncommon in immune activation and similar to that which is found in SLE / systemic lupus erythematosus (The Massachusetts CFIDS Update).

1997

"Myocarditis was a common symptom in an analysis of 1,000 patients of ME/CFS who were seen in Glasgow over the past 20 years*. We were struck by the often-occurring association of patients who develop ME/CFS with acute chest pain resembling a coronary thrombosis. On subsequent clinical follow-up, all these patients had a clinical course that was indistinguishable from patients who presented with Syndrome X. Nuclear magnetic resonance spectroscopy studies of skeletal muscle in patients with Syndrome X show abnormalities that are identical to those found in patients with ME/CFS. We, in examining muscle biopsies of patients with ME/CFS, showed an increase in calcium ATPase activity in skeletal muscles. These data strengthen the relationship between ME/CFS and Syndrome X and suggest that an increased energy expenditure, with a consequent reduction of intra-cellular ATP* (adenosine triphosphate) *and an increase in ATPase activity could account for the abnormalities in these two conditions.* ***Thallium cardiac scans (thallium-210 SPECT scans) in patients with ME/CFS revealed moderate defects in the left ventricle****"* (Arguments for a role of abnormal ionophore function in CFS. A Chaudhuri et al. In: Chronic Fatigue Syndrome. Ed: Yehuda and Mostofsky; Plenum Press, New York, 1997).

1997

"We report the prevalence of abnormal oscillating T waves at Holter monitoring in a consecutive case series of ME/CFS patients from an infectious diseases centre. ***Every ME/CFS patient, but only 22.4% of the non-ME/CFS patients, showed abnormal oscillating T wave flattenings or inversions at Holter monitoring. Abnormal cardiac wall motion at rest and stress, dilatation of the left ventricle, and segmental wall abnormalities were present. Left ventricular ejection fractions, at rest and with exercise, as low as 30% were seen in ME/CFS patients.*** *The abnormal (results) which we confirm here appear to be an essential element to the pathologic physiology of the cardiomyopathy of ME/CFS"* (Cardiac Involvement in Patients with CFS as Documented with Holter and Biopsy Data in Michigan, 1991-1993. AM Lerner et al. Infectious Diseases in Clinical Practice 1997:6:327-333).

This research was summarised by Dr PD Corning, having been reviewed and approved by Dr Lerner:

"***Dr Lerner, an Infectious Diseases specialist at Wayne State University, and his colleagues have found evidence that ME/CFS may be caused by a persistent (virus) infection of the heart***. *This research is significant and well-documented.* ***In this study, 100% of the ME/CFS patients showed abnormal oscillating T waves at 24-hour Holter monitoring*** *and 24% showed weakened function on the left side of the heart (the side that pumps oxygenated blood to all the body except the lungs).* ***The data showed that patients exhibited evidence of cardiomyopathy, or disease of the heart muscle. This finding is so consistent (and) it distinguishes ME/CFS from those with fatigue of unexplained origin. This work offers hard evidence to back up ME/CFS patients' much disbelieved claim that exercise is harmful and causes disease progression in ME/CFS. In many cases, the resulting disease process is progressive. (The virus) attacks the heart tissue producing exercise intolerance, the hallmark of ME/CFS. These researchers have backed up their work with biopsies of the cardiac tissue in ME/CFS patients. They found heart muscle disorganisation, muscle fibre disarray, abnormal formation of fibrous tissue in place of heart muscle cells, fat infiltration and increases in mitochondria within heart muscle cells. All these results are indicative of cardiomyopathy. The weakened heart is aggravated by physical activity, accounting for post-exertional sickness so common in this disease. When the heart muscle tissue is infected, overactivity causes death of cardiac tissue and disease progression. This is in direct conflict with conclusions that ME/CFS symptoms are caused by underactivity due to a sedentary lifestyle***. *Dr Lerner and associates have also documented abnormal fraction ejection in ME/CFS. Normally, over half the blood in the left ventricle is ejected when the left ventricle contracts.* ***In Dr Lerner's subjects, the ejection fraction is decreased. Some patients had a reduced ejection fraction at rest. Others had an ejection fraction that decreased during exercise from 51% to 36%. In a normal subject, the ejection fraction will rise over 5% during exercise. Declining ejection fractions are not seen in normal persons leading sedentary lives".***

The full summary is at http://www.ncf.ca/ip/social.services/cfseir/naneir/news/28FEB98.html .

1998

At the Fourth International AACFS Research and Clinical Conference held in Massachusetts in October 1998, Arnold Peckerman and Benjamin Natelson et al presented evidence of a disorder of the circulation in ME/CFS: as a group, patients with ME/CFS displayed similar cardiovascular function status on most parameters but ***"the results showed that in ME/CFS patients, a lower stroke volume was highly predictive of illness severity: across three different postures, the most severely affected patients were found to have a lower stroke volume and cardiac output compared with those with more moderate illness. These findings suggest a low flow circulatory rate in the most severe cases of ME/CFS; this may indicate a defect in the higher cortical modulation of cardiovascular autonomic control. In the most severely affected, situations may arise where a demand for blood flow to the brain may exceed the supply, with a possibility of ischaemia and a decrement of function".*** (CFS Severity is Related to Reduced Stroke Volume. Peckerman et al. Presented at the Fourth International AACFS Research & Clinical Conference on ME/CFS, Mass. USA).

1999

Watson et al reported that perfusion defects seen in thallium cardiac scans of ME/CFS patients were unlikely to be explained by occlusive coronary vessel disease and that in their studies (as well as in other independent studies), **cardiac thallium SPECT scans were shown to be abnormal in the majority of patients with ME/CFS and perfusion defects were common. Cardiac SPECT scanning is a nuclear medicine technique used to identify regions of under-perfused myocardial tissue** (A Possible Cell Membrane Defect in Chronic Fatigue Syndrome and Syndrome X. Walter S Watson et al. In: Kaski JC (Ed). Chest pain with normal coronary angiogram: pathogenesis, diagnosis and treatment. Kluwer Academic Publishers, London 1999: chapter 13:143-149).

1999

"*This study examined the cardiovascular response to orthostatic challenge. Among subjects who completed the test, those with ME/CFS had higher heart rate and smaller stroke volume than corresponding control subjects.* ***These data show that there are baseline differences in the cardiovascular profiles of ME/CFS patients when compared with control subjects***" (La Manca JJ et al. Clinical Physiology 1999:19:2:111-120).

2000

"The results of this study show enhanced cholinergic activity in the peripheral microcirculation of patients with ME/CFS. Many of the symptoms of ME/CFS, such as temperature sensitivity, gastrointestinal difficulties, problems with sleep, and orthostatic intolerance, are consistent with altered cholinergic activity. ***Our findings might have important implications for features of ME/CFS that involve vascular integrity****"* (V Spence et al. Am J Med 2000:108:736-739).

2001

"Convincing evidence of cardiovascular impairment can be demonstrated" (Research Update presentation to the Alison Hunter Memorial Foundation Third International Clinical and Scientific Conference on ME/CFS held in Sydney, Professor Mina Behan, University of Glasgow).

2001

According to David Streeten, Professor of Endocrinology at Upstate Medical Centre in Syracuse, NY: ***"Inconsistently excessive increases in heart rate were found in ME/CFS patients, in whom venous compliance was significantly reduced*** *(and in whom) delayed orthostatic hypotension was clearly demonstrable, implying impaired sympathetic innervation. Excessive lower body venous pooling, perhaps by reduced cerebral perfusion, is involved in the orthostatic component in these patients"* (Streeten DH. Am J Med Sci 2001:321:3:163-167).

2001

Erich Ryll, Assistant Clinical Professor of Medicine, Division of Infectious and Immunology Diseases, University of California, believes that in ME/CFS there is an infectious venulitis: "*Troublingly (in the literature) very few vascular features were mentioned.* ***I have followed these patients since 1975. Because of this, I have learned all the nuances, all the signs and symptoms of the disease. In studying this disease, one must always have an open mind. This disease teaches the physician to be humble****. The extremity discomfort is often described as a burning, searing sensation. Numbness and tingling of the extremities is common (and) cases have spontaneous bruises that occur without any injury.* ***The disease is frightening to patients because of its severity and its many unusual features. Physicians are not trained to diagnose an illness that encompasses so many signs and symptoms. Two common statements patients make are: 'I hurt all over' and 'I am going to die'. During relapse, many can be totally helpless and unable to care for themselves. Dizziness often occurs and for some patients, it is constant****. They are uncoordinated and lurch about. They state that their legs just give way, causing them to fall.* ***The autonomic nervous system that controls blood vessels is deranged in the disease. Sweating, flushing, icy and blue hands and feet, hot sweaty hands, red and blotchy hands are common. Pain can be the most severe aspect of this disease. There is partial paralysis of the gastrointestinal tract (which) can lead to nausea. Small veins can suddenly rupture. Deep veins can remain inflamed and are not visible on the surface. An electromyogram is frequently abnormal, showing damage to nerves****. The MRI brain image often reveals evidence of demyelination. A SPECT scan invariably shows impairment of brain blood circulation. Muscles may be damaged but do not waste away.*** *There is currently no treatment that can cure this disease. Treatments are geared to making life more bearable*" (http://web.archive.org/web/20080529023815/http://home.tampabay.rr.com/lymecfs/ryll.htm).

2001

*"**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**"* (Inbar O et al. Med Sci Sports Exerc 2001:33:9:1463-1470).

2001

*"**The haemodynamic instability score differed significantly between ME/CFS and other groups**"* (Naschitz JE et al. Semin Arthritis Rheum 2001:31:3:199-208).

2002

According to Peter Rowe, Professor of Paediatrics at Johns Hopkins and an ME/CFS specialist: *"**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**. About a third of ME/CFS studies have identified low urinary and serum levels of cortisol"* (Co-Cure MED: 3rd May 2002; see also Peter C Rowe, Journal of Paediatrics 2002:140:387-388).

2003

***"The main symptom of the ME/CFS patient, i.e. chronic fatigue that is greatly exacerbated by even minor effort, is similar to that of a patient with left ventricular dysfunction**. We performed nuclear ventriculography (MUGA / radioisotopic multiple gated acquisition used to perform a series of dynamic studies of the heart to assess for evidence of abnormalities with myocardial function) stress tests in ME/CFS patients and controls. **During maximal exercise, ejection fraction (EF) increased in controls but declined in ME/CFS patients. The decreases tended to be greater in patients with more severe symptoms. These data support the hypothesis that some cases of ME/CFS may be explained and potentially treated as a problem with left ventricular function**"* (A Peckerman B Natelson et al. FASEB 2003:17:5 Suppl: Part 2: A853).

This study was summarised by Donna Krupa, APS Newsroom, 10th April 2003: *"Growing evidence points to a possible problem with circulation. Studies have found that ME/CFS patients may have reduced blood flow in exercising muscles. A new study provides indication of reduced cardiac function in some patients with ME/CFS. It raises the possibility that some ME/CFS patients may have cardiac disorders that are subtle enough to escape the current net of clinical cardiological diagnoses, but may be significant enough in some patients to lead to the clinical syndrome of ME/CFS".*

2003

*"Cardiovascular reactivity is defined as the change on blood pressure, heart rate, or other haemodynamic parameters in response to physical or mental stimuli. **13 variables showed significant differences between ME/CFS patients and controls.** The degree of arterial stiffness of the large arteries affects both the cardiovascular reactivity and the pulse wave velocity. The FRAS (Fractal & Recurrence Analysis-based Score) differs between the groups of healthy persons, hypertensives, and ME/CFS patients. **The HIS (haemodynamic instability score) distinguished ME/CFS from healthy subjects with 97% sensitivity and 97% specificity.** Based on these data, it appears that the HIS can provide objective criteria (in) the assessment of ME/CFS"* (JE Naschitz et al. Journal of Human Hypertension 2003:17:111-118).

2003

*"**Accumulating evidence points to a problem with circulation in ME/CFS. Although abnormalities in single systems may be insufficient to cause a circulatory dysfunction, cumulatively they could produce significant deficiencies in organ blood flow and symptoms.** We hypothesised that patients with ME/CFS have reduced*

cardiac output. This present study tested this hypothesis using noninvasive impedence cardiography. ***These results provide evidence of reduced cardiac output in severe ME/CFS****. They suggest that in some patients, blood pressure is maintained at the cost of restricted flow, possibly resulting in a low circulatory state.* ***Thus there may be periods in daily activities when demands for blood flow are not adequately met, compromising metabolic processes in at least some vascular compartments. Some percentage of patients (with) ME/CFS may in fact have covert heart disease. The abnormalities causing a reduction in cardiac output in ME/CFS may be dispersed over multiple systems. Even marginal reductions in cardiac output can result in selective underperfusion during activities that increase demand for blood flow. Inquiries should be directed at conditions that may not be overtly expressed in symptoms of ME/CFS, such as underperfusion in the kidneys and the gut, as the organs in which initial conservation of cardiac output takes place.*** *The patients with severe ME/CFS had significantly lower stroke volume and cardiac output than the controls and less ill patients. This study provides indication of reduced cardiac output in some patients with ME/CFS"* (A Peckerman, B Natelson et al. Am J Med Sci 2003:326:2:55-60).

Media coverage of this important paper included the following:

WebMD Medical News: 14th April 2003: ***"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. 'Basically we are talking about heart failure' Peckerman tells WebMD. 'ME/CFS is a progressive disease'. Emory University cardiologist Joseph I Miller III MD, says Peckerman's findings are very interesting (and) he agrees that these patients have serious heart problems".***

2003

"ME/CFS is a debilitating condition of unknown aetiology. Recent studies using brain spectroscopy have revealed metabolic disturbances with significantly elevated choline levels in various regions of the central nervous system. In addition, ***we have recently shown that abnormalities specific to the cholinergic pathway also exist in the peripheral microcirculation of ME/CFS patients (and) our findings might have important implications for vascular integrity in ME/CFS****. ME/CFS is commonly associated with viral onset and immunological disturbance sometimes linked to persistent viral infection. The work described here provides new evidence of disruption to ACh pathways specifically within the peripheral circulation of ME/CFS patients"* (F Khan, V Spence et al. Clin Physiol Funct Imaging 2003:23:282-285).

2004

"Aberrations of cardiovascular reactivity (CVR), an expression of autonomic function, occur in a number of clinical conditions. Recently, a CVR pattern particular to ME/CFS was observed. *Pathological disturbances may alter cardiovascular reactivity. Our data support the existence of disease-related CVR phenotypes. The importance of recognising disease-specific CVR phenotypes may (offer) supporting data for the diagnosis of certain disorders. Recognising the ME/CFS reactivity phenotype has been found useful in supporting the clinical diagnosis of ME/CFS. Furthermore, CVR phenotype may provide an objective criterion to monitor the course of dysautonomia in ME/CFS"* (Naschitz JE et al. QJM 2004:97:3:141-151).

2004

"Research into ME/CFS is hindered by considerable heterogeneity. There has been speculation that many of the neurological symptoms might be cholinergically mediated. As well as these neurological findings, there has been a recent report of autoantibodies specifically to muscarinic receptors in many ME/CFS patients, suggesting that there might be subgroups within the ME/CFS construct that are associated with autoimmune abnormalities of cholinergic muscarinic receptors. Apart from its neurotransmitter functions, acetylcholine is a prominent vasodilator whose action is dependent upon an intact layer of endothelial cells that line the lumen of all blood vessels. In most medical conditions associated with cardiovascular disease there is a blunted response to acetylcholine. However, we have reported increased responses to acetylcholine in the cutaneous microcirculation of ME/CFS patients. There was a

significantly increased response to substance P in ME/CFS patients and this was often accompanied by a spreading flare and localised oedema, a finding not observed in control subjects. (This may be due to) a heightened sensitivity to substance P in terms of its histamine releasing properties. ***Indeed, sensitivity to histamine has been implicated in ME/CFS pathogenesis.*** *The data demonstrated that the dynamics of the acetylcholine-stimulated blood flow response is significantly different in ME/CFS patients compared with control subjects, possibly via a viral mechanism. (This) acetylcholine sensitivity is specific to a sub-group of patients within the ME/CFS construct (and) points to a problem on the vascular endothelium of ME/CFS patients.* ***We are confident that the findings of increased sensitivity to acetylcholine in ME/CFS patients are robust and unusual. Our results are important in terms of vascular control mechanisms in this patient group and may be relevant to the problems of orthostatic instability that is so evident in most ME/CFS patients****"* (VA Spence et al. Prostaglandins, Leukotrienes and Essential Fatty Acids 2004:70:403-407).

2004

"While the cause of ME/CFS remains to be elucidated, extensive literature exists on the role of a variety of infectious agents; up-regulation of anti-viral pathways; immune abnormalities; disruption to the hypothalamic-pituitary-adrenal (HPA) axis; neuropsychological impairments; dysfunction of the autonomic nervous system; oxidative stress; and lipid peroxidation. Looking at the literature as a whole, there are various strands of evidence suggesting that the vascular system in ME/CFS is compromised. *Many ME/CFS patients are unaware that something as simple as being upright can trigger a cluster of symptoms such as dizziness, altered vision, nausea, fatigue, headache, sweating and pallor.* ***Orthostatic intolerance is characteristic of so many of these ME/CFS patients that it could very well serve as a definable subset. It has been suggested by some that orthostatic intolerance in ME/CFS is nothing more than deconditioning associated with bed rest (but) vascular dysfunction appears to be best supported by the data.*** *Some subjects show autonomic dysfunction in their internal organs vasculature (and)* ***evidence points towards enhanced pooling within the internal organs and pelvic circulation.*** *The onset of orthostatic symptoms in many ME/CFS patients is often predated by a viral infection.* ***There is clearly a problem with local vasodilator and vasoconstrictor mechanisms in these patients. There is a significant body of evidence pointing to vascular dysfunction in the peripheral circulation of patients with ME/CFS and this is in addition to blood flow abnormalities within the central nervous system****"* (V Spence & J Stewart. Biologist 2004:51:2:65-70).

2004

Lerner et al demonstrated abnormal cardiac wall motion at rest and in cardiac biopsies: *"A progressive cardiomyopathy caused by incomplete virus multiplication in ME/CFS patients is present"* (Lerner AM et al. In Vivo 2004:18:4:417-424).

2005

A study of adolescents with ME/CFS looked at blood pressure, arterial stiffness and arterial wall thickness. Arterial stiffness, expressed as common carotid distension, was lower in adolescents with ME/CFS, indicating stiffer arteries. *"Pain perception differed considerably between patients and controls (and) this is the first study to confirm this difference. The unexpected finding of stiffer arteries in patients with ME/CFS warrants additional investigation"* (EM van de Putte et al. Paediatrics 2005:115:4:415-422).

2005

"Orthostatic intolerance certainly causes breathlessness. ***The cause of the breathlessness is probably a reduction in blood flow through the heart and lungs. Patients with ME/CFS cannot hold their breath as long as healthy people.*** *This was first noted by Dr Paul Cheney"* (DS Bell. http://www.davidsbell.com/LynNewsV2N2.htm).

2005

On 10th April 2005 Carol Sieverling posted on the internet (Co-Cure) "The Heart of the Matter: CFS and Cardiac Issues" – a 41 page exposition of Professor Paul Cheney's experience and expertise, from which the following notes are taken and to both of whom grateful acknowledgement is made.

Cheney's focus is based on the paper by Dr Ben Natelson (clinical neurologist and Professor of Neurology) and Dr Arnold Peckerman (cardiopulmonary physiologist) at New Jersey Medical Centre (ref: "Abnormal Impedance Cardiography Predicts Symptom Severity in Chronic Fatigue Syndrome": Peckerman et al: The American Journal of the Medical Sciences: 2003:326:(2):55-60).

This significant paper says that, without exception, every disabled CFIDS (i.e. ME/CFS) patient is in heart failure.

There are two kinds of heart failure: one that any cardiologist can diagnose in about a minute (which ME/CFS patients do not have); the other is Compensated Idiopathic Cardiomyopathy (CIM). Given that at least 35% of those with CIM will die within 5 years unless they receive a heart transplant, but given that in 20 years' experience of ME/CFS Cheney has never seen one patient go on to transplant, why aren't those with ME/CFS-induced CIM not dead? Cheney believes it is because ME/CFS itself is protecting patients from a deeper problem that is often missed because it is so well-hidden.

The problem

The New Jersey team looked at many things in ME/CFS patients and they found something: a "Q" problem. "Q" stands for *cardiac output in litres per minute*. **In ME/CFS patients, Q values correlated -- with great precision – with the level of disability.** Q was measured using impedance cardiography, a clinically validated and Government agency-recognised algorithm that is not experimental.

Normal people pump 7 litres per minute through their heart, with very little variance, and when they stand up, that output drops to 5 litres per minute (a full 30% drop, but this is normal). Those two litres are rapidly pooled in the lower extremities and capacitance vessels. Normal people do not sense that 30% drop in cardiac output when they stand up because their blood pressure either stays normal or rises -- the body will defend blood pressure beyond anything else in order to keep the pulse going. This is critical to understanding what happens in ME/CFS patients.

However, **what the New Jersey team found in people with ME/CFS was astonishing – 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).**

The disability level was exactly proportional to the severity of their Q defect, without exception and with scientific precision.

Symptoms

The New Jersey team then looked to see if there were any symptoms that were observable in disabled ME/CFS patients but not in others and they found that there was only one such symptom that was seen in patients with a Q problem: post-exertional fatigue. To quote Cheney: "That is, **when you push yourself physically, you get worse"**.

ME/CFS patients have a big Q problem; to quote Cheney again: "**all disabled ME/CFS patients, all of whom have post-exertional fatigue, have low Q and are in heart failure"**.

Post-exertional fatigue (long documented as the cardinal feature of ME/CFS but not of non-specific states of chronic fatigue) is the one symptom that correlates with Q. **Among disabled ME/CFS patients, 80% had muscle pain; 75% had joint pain; 72% had memory and concentration problems; 70% had unrefreshing sleep; 68% had fever and chills; 62% had generalised weakness; 60% had headaches, but 100% had post-exertional fatigue.**

In Cheney's model, symptoms in ME/CFS reflect the interaction between Q and how the body compensates for too low a Q, so depending on the nature of the compensation (which is individually distinct), there is an array of symptoms that is individually determined and which will arise out of factors unique to each person.

Cheney posits that when faced with a low Q, the body sacrifices tissue perfusion in order to maintain blood pressure: ie. microcirculation to the tissues of the body is sacrificed to maintain blood pressure so that the person does not die in the face of too a low Q. **This compensation is what is going on in the ME/CFS patient.**

In the Peckerman study, the data on the disabled ME/CFS patients reveals that even when they are lying down, their Q is only 5 litres per minute (not 7 as in normals). When disabled ME/CFS patients stand up, the Q of 5 litres per minute drops to 3.7 litres per minute, so these patients do not have adequate Q to function. The lower the Q, the more time the patient will spend lying down because lying down is the only time they come close to having sufficient cardiac output to survive.

Compensated Idiopathic Cardiomyopathy

Cheney states that it is important to note that the body does not sacrifice tissue perfusion equally across all organ systems: instead, it prioritises the order of sacrifice and one can observe the progression of ME/CFS by noting this prioritisation.

Two organ systems in particular have a protective mechanism (the Renin Angiotensin System, or RAS) against restricted tissue perfusion: the lung and the kidneys. These organs can sustain the greatest degree of Q problems because of this extra protection. Additionally, the heart and the brain also have this extra protection, even in the face of an extremely low Q. Therefore the lung, the brain, the kidneys and the heart are a bit more protected than the liver, the gut, the muscles and the skin from a drop in Q.

In what order is tissue perfusion sacrificed, and what are the consequences? Certainly, Cheney's submission seems to tally with the experience of long-term ME/CFS sufferers.

The first is the skin: if the microcirculation of the skin is compromised, several problems can arise. One is that without adequate microcirculation to the skin, the body cannot thermoregulate anymore: the patient cannot stand heat or cold and if the core temperature rises, the patient will not be able to sleep and the immune system will be activated. In order to regulate that problem, the body will activate thyroid regulation which will down-regulate in order to keep the body temperature from going too high. The result of this is that the patient develops compensatory hypothyroidism, which means that now the patient will have trouble with feeling cold. Also, the body will not be able to eliminate VOCs (volatile organic compounds), which are shed in the skin's oil ducts, so VOCs build up in the body's fat stores and the patient becomes progressively chemically poisoned by whatever is present in the environment -- **in other words, the patient develops Multiple Chemical Sensitivity (MCS).**

The second effect: if things get worse, **the next microcirculation to be sacrificed is that to the muscles and the patient will have exercise intolerance and s/he cannot go upstairs**. If things get still worse, the patient begins to get fibromyalgic pain in the muscles. Cheney posits that if microcirculation to the joints becomes compromised, it may precipitate pyrophosphoric acid and uric acid crystals and the patient starts to have arthralgia linked to this circulatory defect.

The next system to be compromised is the liver and gut. **One of the first things the patient may notice in this stage of disease progression is that there are fewer and fewer foods s/he will be able to tolerate, partly because microcirculation is necessary for proper digestion. Also the body will not secrete digestive juices so whatever food is tolerated will not be properly digested: if food cannot be digested, there will be peptides that are only partially digested and therefore are highly immune-reactive; they will leak out of the gut into the bloodstream, resulting in food allergies and / or sensitivities**. The body will be unable to detoxify the gut ecology, so the gut will begin to poison the patient, who will feel a sense of toxic malaise, with diarrhoea, constipation, flatulence and all kinds of gut problems. If this gets worse, a malabsorption syndrome will develop, resulting in increasing toxicity in which the patient feels "yucky" and which can manifest as a variety of skin disturbances (for instance, a rash), as well as problems in the brain.

The fourth affected system is the brain: **Cheney posits that there is a devastating effect in the brain as a result of liver / gut dysfunction, which can quickly toxify the brain**, resulting in disturbances of memory and of processing speed. **Also, the hypothalamus begins to destabilise the patient from the autonomic nervous system perspective. In all probability, the brain and heart suffer simultaneous compromise, but patients usually notice the brain being affected much earlier than the heart – this is because heart muscle cells have the greatest mitochondrial content of any tissue in the body, so when the mitochondria are impaired, the heart muscle has the greatest reserve.** Even if the patient is sedentary with not too much demand on the heart, s/he can still think and make great demands on the brain, and energy is energy, whether it is being used physically or cognitively.

The fifth affected system is the heart: Cheney posits that the effect of compromised microcirculation upon the heart has an "a" part and a "b" part: part "a" is the manifestation of microcirculation impairment and part "b" is "the event horizon".

Part "a": manifestation of microcirculation impairment: **the initial manifestation of microcirculatory impairment of the heart is arrhythmia with exercise intolerance: when the patient goes upstairs, more cardiac output is needed but the patient cannot sustain it.** As it gets worse, there will be mitral valve prolapse (MVP) because of inadequate capillary function. **Finally, when there are even more severe microcirculatory problems, the patient starts to get chest pain as the myocardial cells die because they cannot get adequate oxygen.**

Part "b": the event horizon: (once this line is passed, there is no going back): Cheney's view is that the "event horizon" with respect to the heart is this: when the microcirculation defect within the heart itself begins to impact Q itself, a vicious circle begins – microcirculation impairment reduces the Q, which produces more microcirculation impairment, which produces even more Q problems, so **down goes the patient into the next phase of cardiac failure, which is the lung.**

The sixth affected system is the lung and kidney: **cardiac failure in the lung produces congestive heart failure (CHF) and pulmonary oedema, then the kidney is affected (the kidney is the last to go because it has the RAS back-up system). Combined with liver impairment, this stage is known as hepatorenal failure, which is the requisite cause of death due to Compensated Idiopathic Cardiomyopathy.**

Cheney said "*How will a patient know if s/he eventually loses the ability to compensate? They will know it if when they lie down, they are short of breath*".

Cheney comments on Professor Martin Pall's work on the role of peroxynitrite in ME/CFS. Uric acid is a powerful scavenger of peroxynitrite, as is uric acid. Cheney has measured uric acid levels in ME/CFS patients and has found them to be amongst the lowest levels he has ever measured in his entire medical career.

Cheney notes that Dr Les Simpson in New Zealand found that the red blood cells of patients with ME/CFS were deformed and when deformed, they cannot get through the capillary bed and so cause pain. An indication of such deformity is a drop in the sedimentation rate (SED, or ESR) and **Cheney has observed that when measured in a laboratory, ME/CFS patients' sedimentation rate is the lowest he has ever recorded, which confirms to Cheney that ME/CFS patients have an induced haemoglobinopathy. He believes that the ME/CFS patients with the lowest sedimentation rate may have the greatest degree of pain.** The more deformed the red blood cells, the more pain may be experienced. **Some ME/CFS patients have a problem similar to that of sickle cell anaemia in this regard, and sickle cell patients have unbelievable pain.** Cheney emphasises that it is bad enough when patients do not perfuse their muscles and joints (because of poor microcirculation) but it is even worse when red blood cells are so deformed that they can barely get through the capillaries or are blocked entirely.

Cheney notes that in the Laboratory Textbook of Medicine, there are only three diseases that lower the sedimentation rate to that level: one is sickle cell anaemia (a genetic haemoglobinopathy); the second is ME/CFS (an acquired haemoglobinopathy) and the third is idiopathic cardiomyopathy.

Cheney observes that 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. **He notes that some ME/CFS patients need to lie down all the time to augment their blood volume in order to survive.** He has found increasing the intake of potassium to be helpful (potassium induces aldosterone, a hormone that significantly increases blood volume), and that magnesium is beneficial as it is a vasodilator and helps reduce the resistance the blood encounters.

Cheney is at pains to emphasise that none of these measures is a cure -- they are simply means to help patients disabled with ME/CFS remain as functional as possible.

(Cheney's credentials include more than two decades' experience treating over 5,000 ME/CFS patients in 15 countries; research positions relevant to ME/CFS with the US Centres for Disease Control, Emory University and the University of Pennsylvania, and numerous journal articles. He was a founding director of the International Association of Chronic Fatigue Syndrome, an association of scientists and clinicians).

2005

"There is mounting evidence that oxidative stress and lipid peroxidation contribute to the disease process and to some of the symptoms (in ME/CFS). *While free radicals may generate tissue injury, it is also evident that other oxidative by-products, especially isoprostanes, can exert potent biological activity and act as a powerful vasoconstrictor of the peripheral vasculature. Such biological effects may be instrumental in the development of some of the vascular features that characterise patients with ME/CFS.* ***The novel findings of this study are that patients with ME/CFS have significantly elevated levels of F_2-isoprostanes alongside other key markers of oxidative stress, and that these correlate with various ME/CFS symptoms****. This is the first time that elevated levels of isoprostanes have been reported in patients with ME/CFS. Isoprostanes have potent biological effects associated with increased cell permeability. They have also been shown to be powerfully vasoconstricting and are involved in endothelial injury.* ***Exercising muscle is a prime contender for excessive free radical generation, with recent evidence pointing to good correlations between muscle pain thresholds and fatigue with various blood markers of oxidative injury in ME/CFS patients, and further evidence of viral persistence in muscle tissue in some patients with the illness. Research evidence has demonstrated that incremental exercise challenge potentiates a prolonged and accentuated oxidative stress that might well account for post-exercise symptoms in ME/CFS patients.*** *It could be suggested that ME/CFS is an inflammatory condition with many patients in a pro-oxidant states, and this could explain many of the pathological manifestations that underlie the illness"* (G Kennedy, VA Spence et al. Free Radical Biology & Medicine 2005:39:584-589).

2005

Researchers at the US Centres for Disease Control (CDC) reported that patients with ME/CFS exhibited scores on assessment tools that quantify impairment and symptoms occurrence, duration and severity and were able to be identified with precision. **The authors reported that the ME/CFS patient exhibited scores similar to patients with congestive heart failure** (WC Reeves et al. BioMed Central Medicine, 15th December 2005).

2006

Researchers used serial cardiopulmonary exercise tests to support a diagnosis of ME/CFS. The authors noted: *"In the absence of a second exercise test, the lack of any significant differences would appear to suggest no functional impairment in ME/CFS patients. However, the results from the second test indicate the presence of an ME/CFS related post-exertional malaise. It might be concluded that a single exercise test is insufficient to demonstrate functional impairment in ME/CFS patients. A second test may be necessary to document the atypical recovery response and protected malaise unique to ME/CFS"* (VanNess MJ et al. Medicine & Science in Sports & Exercise 2006:38:5: Suppl: S85).

2006

In his September 2006 seminar (available on a two-DVD boxed set from videos@dfwcfids.org), **Professor Paul Cheney again warned that aerobic exercise may kill the patient with ME/CFS. As before, Cheney acknowledges his debt to the work of Peckerman. Cheney noted that there is an objective database in key medical literature that includes evidence of diastolic dysfunction and heart failure in ME/CFS.**

There are two types of heart failure: systolic (which is a failure to eject) and diastolic (which is not a failure to eject, but a failure to fill properly). Diastolic heart failure was first described in the 1980s but there was no significant literature until the 1990s, and no significant way to measure it until 2001.

Whilst there has been little recognition of the existence of diastolic dysfunction by some cardiologists (considered a relative rarity in 1986), in 2006 an article entitled "Diastolic heart failure – a common and lethal condition by any name" was published by Gerard Aurigemma, who concluded that: "*the development of specific, effective management approaches for diastolic heart failure must become a high priority*" (NEJM 2006:355:3:308-310). The NEJM carried a significant paper on more than 4,500 patients studied with diastolic heart failure; this increase is unexplained, but is accelerating, and Cheney wonders if it is in fact an explosion of ME/CFS.

Oxidative stress links ME/CFS to fibromyalgia, multiple chemical sensitivity and Gulf War Syndrome.

Cheney says that on physical examination:

In phase 1: (immune activation) one sees

- lymphyodynia (seen in 80-90%)
- crimson crescents bilaterally on soft palate (seen in 80%)
- sub-normal temperature

In phase 2: one sees

- evidence of subcortical brain injury
- vestibular dysfunction (seen in 94%)
- hyper-reflexia, especially of the knees and ankles (seen in 70%)

In phases 3 and 4: the most interesting are the metabolic disturbances:

- there is shortened breath-holding capacity (seen in 60%)
- there is very poor oxygen transport (seen in 90%): pulse oximetry readings measuring saturation of haemoglobin show a significant inhibition to desaturate
- there is finger-print destruction (seen in 50%): cross-hatching occurs, with degradation of the ridges; punch biopsies found perivascular lymphoid infiltrates ie. an inflammatory cuffing exactly as seen in lupus, which signifies a non-specific immune activation issue (so the finger-print changes could be reflecting much more than just loss of finger-prints and may represent a vasculopathy)
- there is sub-normal temperature (seen in 80%)
- there is low systolic blood pressure (in 50% of patients it is less than 100mmHg)
- there is orthostatic B/P or pulse changes (seen in 70%)

These findings portend significant physiological issues, chief of which is that oxygen is being prevented from getting into the cell, and if there is no oxygen, there is no energy.

On Magnetic Resonance Spectroscopy:

- 70% of patients show elevated lactate levels in the ventricular system (the lactate elevation is not normal and indicates a defect in energy in the brain: ME/CFS patients have significantly elevated lactate levels and the fatigue correlated significantly with the level of lactate)
- 10% have evidence of neuronal destruction and elevated choline peaks, typically in the perivascular areas

On Magnetic Resonance Imaging:

- 78% of patients have punctate lesions which are most consistent with small strokes and there is evidence to support this

Mixed venous blood gas picture:

- P_vO_2 is 25 (it should be 40)
- P_vCO_2 is 55 (it should be 45)

This is a differential hypoxia with hypercarbia. **There are only two diseases where this is seen: one is pulmonary hypertension; the other is ME/CFS.**

Cheney asks where does the oxygen go? It is being transported somewhere, but not to the mitochondria. ME/CFS patients have been shown to have increased pooling of extra-cellular fluid in the belly, pelvis and legs which might contain this dissolved oxygen, but it is more likely being consumed by the oxidative pathway to create superoxide in massive amounts. Superoxide is the progenitor of all free radicals. The consequences are increased intra-cellular oxidative stress.

Cheney says there are problems at cell level in energy production, and because of this degraded energy problem, patients suffer a defect in the ability to detoxify toxins, especially in the portal circulation (giving rise to gut toxicity as seen in phase 2). **Gene alterations (seen in phase 4) generate a massive disturbance in the development of energy at the cell level.** If you lose energy, you lose glutathione, but the more glutathione you give, the more you just create oxidised glutathione, which generates loss of citrate, causing a left shift on oxyhaemoglobin desaturation. Citrate also binds to magnesium, so over time the patient will develop a severe magnesium depletion syndrome. (Cheney says that when that happens: "*you've had your last good night's sleep: when you lose magnesium, you can't sleep any more*").

In ME/CFS, these serious issues are a big problem, especially in the brain, the heart and in muscle. 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.

Prolonged energy deficits can cause semi-permanent DNA phenotype adaptations and complications can occur, especially within energy-sensitive systems such as the heart, the brain and the muscles.

In ME/CFS, catalase is deficient in the heart, lungs and liver (catalase is the most protective enzyme in the body against the ravages of superoxide), and Cheney noted that electromagnetic fields [EMFs] "*screw up*" superoxide dismutase (SOD), which is a major anti-oxidant scavenger.

Cheney reports that echocardiograms (sonograms of the heart) indicate that as many as 99% of his ME/CFS patients test positive for some level of diastolic dysfunction.

ME/CFS patients have a high heart rate but a low cardiac output. In ME/CFS there is a cardiac dimension that is independent of (but not excluding) autonomic function or blood volume.

82% of patients have abnormal cardiac impedence.

Cheney says that at least half of patients exhibited atrial cavitation, and that when these patients stood up, in 80% the filling volume collapsed. He tested this with magnesium and the results were significant: magnesium restored 12% of energy in one minute. Magnesium affects the intracellular energetics, proving that patients have a "tremendous" energy problem that is very sensitive to magnesium. (The reason magnesium is so important is that without it, ATP cannot be converted to ADP for the production of energy).

Cheney says that ME/CFS patients "*squeeze the hell"* out of their left ventricle, resulting in a "*whopping"* 70% increase in left ventricular wall motion thickness. The reason why patients are squeezing so hard is because they do not have enough energy to fill the chambers of the heart properly so they are trying to compensate by squeezing a lot harder (ie. the way patients are compensating for this loss of cardiac output is by squeezing the left ventricle much harder).

There are significant consequences of this. **One consequence is that ME/CFS patients become asynchronised (i.e. the heart can be filling and ejecting at the same time).**

If out of synchrony, the ventricle cannot cope, so cardiac output is severely degraded.

A second consequence is that patients develop a strain pattern, which is an indication of ischaemia. **Cheney has seen ischaemic changes in the inner ventricular wall because of the increased squeezing.**

It is increasingly clear that in ME/CFS, a diminished threshold for oxygen toxicity exists, and that each patient will have a unique threshold. These findings have a significant negative effect on Accident & Emergency and operating theatre uses of oxygen during surgery, because an ME/CFS patient could be given too much oxygen and be killed on the operating table.

There is a difference between diastolic dysfunction and diastolic failure: in diastolic dysfunction there is a filling problem but the body is compensating for it and achieving enough cardiac output to match metabolic demand.

Diastolic failure begins when the body can no longer compensate and there is a reduction in cardiac output. Cheney repeated that this is seen in 80% of ME/CFS patients.

If patients draw down their lifestyle to live within the means of the reduced cardiac output, then progression into congestive cardiac failure (CCF) is slowed down, but if things continue to progress, a point will be reached where

there is no adequate cardiac output, and dyspnoea will develop, with ankle oedema and other signs of congestive cardiac failure.

The message from Cheney is clear: 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.

According to Cheney, it is difficult to talk about a low cardiac output without talking about the involvement of the brain and the adrenal glands.

If the cardiac output goes down, in order not to die, there is a rise in noradrenergic tone (also involving the adrenal glands) to bring the output back up. **In ME/CFS, this is a serious problem, because when the adrenals are exhausted, there *will* be low cardiac output.**

There is no such thing as an ME/CFS patient who is NOT hypothyroid: this has nothing to do with thyroid failure, but everything to do with matching metabolic demand and cardiac output.

A mismatch between metabolic demand and cardiac output, even very briefly, will kill. A major cause of death in ME/CFS is heart failure.

2007

The 8th International Association of Chronic Fatigue Syndrome (IACFS) Conference was held at Fort Lauderdale, Florida, from 10th-14th January 2007. The following extracts are taken from "Facts from Florida" (http://www.meactionuk.org.uk/Facts_from_Florida.htm).

- the conference was attended by over 250 clinicians and researchers from 28 different countries and there was a strong sense that they were all co-operating to build on the science. **It is the science that has freed the world from any doubt that ME/CFS is a legitimate disease with an aetiology that is not rooted in the psyche -- Japanese and Swedish research teams collaborated in a comprehensive study of a neuro-molecular mechanism and concluded that ME/CFS is an organic disorder. It was described as "this miserable illness"**

- the latest figures (January 2007) on the economic impact of ME/CFS in the US are between $22 billion and $28.6 billion annually; in Japan, the figure is over $10 billion annually. The Japanese Government recognises ME/CFS as a real threat not only medically but also economically and has initiated a large research programme into causation and treatment

- **one of the most striking elements was the convergence of research findings: the three areas that came up again and again were inflammation, mitochondrial abnormalities, and vascular problems**

- **three separate research teams found evidence of microvascular problems in ME/CFS**

- **the significant confluence of findings on elastase (a protease enzyme, i.e. it digests and degrades a number of proteins, including elastin, a substance that supports the structural framework of the lungs and other organs); vascular problems; apoptosis (programmed cell death); free radical production (highly damaging to DNA, to cell membranes and to proteins) and inflammation was undeniable**

- in ME/CFS, testing for elastase, RNase-L, C-reactive protein, selected cytokines and NK cell activity are recommended because they are objective markers of pathophysiology and severity. In addition, **an exercise test/re-test of cardiopulmonary function is necessary because it is 100% objective and**

confirms reduced functional capacity as well as post-exertional malaise for disability purposes. Further, lipid abnormalities and evidence of metabolic syndrome should be looked for

- researchers are developing methods to measure cardiovascular and cardiopulmonary health in ME/CFS patients, which relates to oxygen consumption

- ME/CFS patients' ability to work is impaired, as shown by an abnormal exercise stress test. Margaret Ciccolella and Christopher Snell et al from Stockton, CA, demonstrated that patients show extreme abnormalities in a next-day/second session of exercise. They do not recover in 24 hours. In one study, only one patient had recovered to baseline within 48 hours. These changes in serial testing point to a significant and confirmable physical abnormality, verifying the cardinal symptom of post-exertional malaise. **This test/retest exercise test is 100% objective and can prove to the disability companies that ME/CFS is neither malingering nor faking. In ME/CFS patients, the measurements declined by about 25%, far more than in other significant diseases such as COPD and even heart failure**

- **post-exertional malaise following exercise challenge results in fatigue, light-headedness, vertigo, joint pain, muscle pain, cognitive dysfunction, headache, nausea, trembling, instability, and sore glands**

- i**n ME/CFS patients, there is cellular hypoxia — oxygen is delivered to the cells of the heart, brain, skeletal muscle and other organs, but the process of turning oxygen into energy is derailed**

- **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**

- a US NIH-funded trial by Professor Barry Hurwitz, a colleague of Professor Nancy Klimas at the University of Miami, found that 70% of ME/CFS patients have a low red blood cell volume. **Treatment to increase blood volume was ineffective in respect of exercise tolerance and fatigue**

- one of the highlights of the conference was the presentation of Dr Vance Spence's work (University of Dundee) on inflammation and arterial stiffness in patients with ME/CFS **– arterial stiffness is rarely found in adolescents, but in ME/CFS these young patients had higher levels of arterial stiffness than diabetic patients. This work looked at inflammatory factors (free radical by-products and C-reactive protein, an inflammatory marker) and found abnormally high levels of free radical by-products and C-reactive protein in patients but not in controls. C-reactive protein levels were significantly correlated with increased arterial stiffness.** A likely cause is elastase. Elastase is a central factor in Professor Kenny de Meirleir's RNase-L paradigm (see below), and Dr Baraniuk's cerebrospinal fluid proteome study suggests elastase is implicated in blood vessel problems in the brain of ME/CFS patients. The logical consequences of increased arterial stiffness are exercise intolerance and diastolic (cardiac) dysfunction. The circulatory problems seen in ME/CFS may originate in endothelial cells lining all blood vessels. These cells are involved not only in opening and closing blood vessels but in the immune response as well, and they are often attacked by pathogens

- Professor Paul Cheney presented evidence of diastolic (cardiac) dysfunction in ME/CFS. This results in hypoxia (low oxygen levels relative to metabolic needs)

- **Cheney stated that 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**

- Professor Mark VanNess from the University of the Pacific found that maximum aerobic capacity (VO_2 peak) is reduced in ME/CFS compared with sedentary controls

- Van Ness found that oxygen capacity at the anaerobic threshold is reduced in ME/CFS

- Van Ness also found that serum lactate is elevated, suggesting an abnormally early shift to anaerobic metabolism

- in a subset of patients, Martin Lerner (Wayne State University, Detroit) described persistent EBV and/or CMV in ME/CFS patients: in addition to having high titres, all 37 patients studied had an elevated heart rate at rest, recurrent T-wave inversion on Holter monitoring, cardiac abnormalities and/or biopsy-proven cardiomyopathy. Symptoms included not only tachycardia but chest pain and syncope

- **according to Lerner, all ME/CFS patients have abnormal T waves; inversion is seen in 96%; there is resting tachycardia. Cardiac biopsies show fibrosis, myofibre disarray and fatty infiltrates.**

Other key areas of ME/CFS research reported in "Facts from Florida" include Nuclear Medicine (showing some of the abnormalities in functioning that patients with ME/CFS experience on a daily basis); Proteomics (the study of proteins made in the cell, including evidence of unique markers in the cerebrospinal fluid of ME/CFS patients that are completely absent in controls and which were described as *"unbelievable"*); Virology (showing evidence of viral persistence in ME/CFS patients); Gastrointestinal dysfunction (evidence was presented of enterovirus in stomach biopsies of 80% of ME/CFS patients, compared with none in controls); Sleep disruption (due to a lack of parasympathetic activity during attempted sleep periods); Pain (described as a major feature in many aspects of ME/CFS); Cognitive impairment (evidence was presented suggesting that the central nervous system correlates of cognitive dysfunction in ME/CFS have an inflammatory basis); Immunology (evidence of activated CD8 cells; poorly functioning NK cells; novel findings – seen only in ME/CFS – of abnormalities of the 2-5A pathway [RNase-L ratio]; cytokine abnormalities [pro-inflammatory dysregulation]; increased TGF, and 27 times more circulating immune complexes than in controls); Neuroendocrine dysfunction (evidence of neurobiological distinctions between 'pure' ME/CFS and CFS/ME with psychiatric morbidity -- further evidence that ME/CFS is not psychiatric in origin); Genomics (the study of the function and interactions of genetic material, including interactions with environmental factors which play a significant role in ME/CFS) and Paediatrics (with the presentation of new paediatric diagnostic criteria from Professor Leonard Jason et al, which means there is now a science-based instrument to correctly diagnose children and adolescents with ME/CFS).

In summary, this international conference demonstrated the difference between science and psychiatry.

2008

A Scottish team noted that as long ago as 1997, markers of inflammation were demonstrated in some patients with ME/CFS, and that in 2005, vascular stiffness was shown to have an impact on resting and exercise-induced haemodynamics. **Aware of the accumulating evidence that the cardiovascular system is compromised in many patients with ME/CFS, this team investigated the relationship between inflammation and arterial stiffness in ME/CFS patients**. (If arteries become stiff, the heart has to work harder and, ultimately, blood pressure becomes higher. Stiff arteries have been linked to kidney problems and heart disease, and may contribute to the orthostatic problems (dizziness on standing) experienced by some ME/CFS patients). **This study demonstrated that the augmentation index (a measure of arterial stiffness) was significantly greater in patients with ME/CFS than in controls and concluded: "***The results of this study have shown that patients with ME/CFS have high serum CRP levels* **(C-reactive protein, a sensitive biochemical marker of inflammation)** ***indicative of chronic inflammation. The combination of increased arterial wave reflection, inflammation and oxidative stress may result in unfavourable***

haemodynamics and an increased risk of a future cardiovascular event in these patients" (VA Spence et al. Clinical Science 2008:114:561-566).

2009

At the IACFS International Research Conference held in March 2009 at Reno, Nevada, Drs Allan and Kathleen Light and Dr Lucinda Bateman presented evidence that adrenergic and sensory receptor expression on leucocytes increases after moderate exercise in both (ME)CFS and fibromyalgia. Sensors that monitor muscle health are found on leucocytes (white blood cells) and continually monitor the blood for signs of muscle damage (eg. for increased levels of lactate, for low pH and for purines that are produced during ATP production). Drs Light tested receptor activity at baseline and at varying times after moderate exercise in (ME)CFS patients. At baseline, receptor activity was similar in both (ME)CFS and FM patients, apart from a few receptors suggesting that (ME)CFS patients had increased vascular resistance (suggesting that blood vessels were narrowed). **The post-exercise receptor activity was dramatically different in (ME)CFS patients**; whereas in controls, the receptor activity barely changed after exercise, in (ME)CFS patients, *"they look like Mt Vesuvius. (ME)CFS patients often feel like they've run a marathon after mild exercise; these results suggested that at least one part of their body reacted as if they had"*. Intense exercise usually caused receptor activity to increase **several hours later** in healthy people, but even mild exercise caused the receptor activity to increase in **just 30 minutes** in (ME)CFS patients. Not only did the receptors appear to be over-reacting in (ME)CFS patients, but they also appeared to be responding surprisingly quickly. **Beginning at 30 minutes after exercise and continuing at 8, 24 and 48 hours after exercise, (ME)CFS patients showed increases of ion channel receptor activity up to four times the pre-exercise level, while healthy subjects showed no increase at all.** The activity of a receptor that is implicated in pain **doubled** in (ME)CFS patients who also had FM, but showed no increase at all in healthy subjects. Sympathetic nervous system (adrenergic) receptors that detect SNS activity were increased **2 – 6 times**. **(ME)CFS patients appear to have many times the normal level of these receptors on their white blood cells and remarkably, these receptors were still highly over-reactive 48 hours after mild exercise**. The graph of the results was described as "incredible", and Professor Nancy Klimas commented: *"That was a great study"* (with grateful acknowledgement to Cort Johnson: Co-Cure MED: 4th October 2009: http://aboutmecfs.org/Conf/IACFS09Surprise.aspx).

Two important questions relating to the PACE Trial remain unanswered: (i) are the West Midlands MREC and the peer reviewers at the MRC who approved the PACE trial protocol certain that the incremental exercise component poses no harm for people with ME/CFS and (ii) have all MRC trial participants been screened for cardiovascular anomalies before starting the trial, or are the Principal Investigators content to rely on the certainty that they themselves can never be held accountable for any harm to any patient, since all participants must sign a compulsory waiver, which means that no participant can ever pursue any claim for medical negligence or damages?

Documented neurological abnormalities in ME/CFS

1962

ME/CFS was included by the distinguished neurologist Lord Brain in his textbook "Diseases of the Nervous System", Oxford University Press, sixth edition: pp355 " *(ME) is the term applied to a disorder which has been recognised in many parts of the world. Its features are the severity of the symptoms in relation to the slightness of the physical signs. A characteristic feature of the muscular weakness is the intermittency of power of muscular contraction. Changes which are believed to be characteristic have been found on electromyography. A striking feature is the tendency for relapses to occur during the months, and in some cases even years, after the infection".*

1990

Extract from a Press Conference by Professor Paul Cheney held in San Francisco in September 1990 and reported in CFIDS Chronicle, September 1990:

"***I believe this is a disease that affects the central nervous system (CNS) and I'll show you some slides to help convince you of that. We are going to (look at) what evidence there is for neurologic disease in these patients***. *This is a study done by Dr Carolyn Warner from the Dent Neurologic Institute in Buffalo, New York, which specialises in multiple sclerosis.* ***Some people think that (ME)CFS can look like MS and there are clinical features that are overlapping. The most specific neurologic symptom is dysequilibrium. These patients have a balance disturbance and on certain simple neurologic tests they fall over. On more sophisticated neurologic tests of vestibular function they are often grossly abnormal. Nearly every patient had something abnormal within the central nervous system, and also neuromuscular problems, or muscle itself.*** *These patients are cognitively impaired and you can prove it by formalised psychometric tests.* ***Other evidence of CNS involvement can be demonstrated by tests looking directly at the CNS.*** *These are slices of brain created by using magnetic resonance imaging.* ***These inflammatory and/or demyelinating plaques can be seen in the white matter, in the cerebellum and white matter tracts throughout the high cerebral convexities and in the frontal lobes. Over half of (ME)CFS patients will typically show lesions within the central nervous system.*** *Professor Ismael Mena, chairman of the Department of Nuclear Medicine at Harbourview UCLA Medical Centre, found that there were defects in perfusion of temporal lobes primarily. He looked at regional cerebral blood flow and found that in (ME)CFS patients compared to controls, there was a diminishment of cerebral blood flow in the right temporal lobe that was significant.* ***In other words, blood flow to the right temporal lobe was impaired in these patients. The temporal lobe seems to get really hit by this disease. I want to point out that 71% of patients with (ME)CFS are abnormal by this technique***".

1991

"Patients with (ME)CFS often complain of dysequilibrium. Data suggests that their symptoms of dysequilibrium can be substantiated with quantitative laboratory testing. The abnormalities are more suggestive of CNS deficits than of peripheral vestibular deficits" (JMR Furman. Rev Inf Dis 1991:13: (Suppl 1):S109-111).

1994

In a CME (continuing medical education) credit article, Dr David Bell, an internationally-acclaimed paediatrician specialising in ME/CFS, wrote in Postgraduate Medicine: "***Findings now point to CNS involvement***: *Recent research has yielded remarkable data (and has) provided a steady current of scientific additions to our understanding of (ME)CFS"*. Reviewing the immunological abnormalities (and noting that the patients who were the most disabled had the highest levels of interleukin-1), Bell pointed out that a consistent pattern of immune dysfunction is emerging, which helps to characterise and define the illness. He noted the elevated levels of cytokines, particularly those that affect neuronal tissue. He reviewed the evidence for retroviral markers, the pituitary and hypothalamic abnormalities, and the neuroendocrine abnormalities. He reviewed the cerebral perfusion abnormalities and highlighted the importance of elevated serum ACE levels seen in ME/CFS: ***"Another addition to the bewildering array of laboratory abnormalities found in patients with (ME)CFS is an increased serum concentration of angiotensin-converting enzyme (ACE). This is a marker not only for sarcoidosis but also for diseases involving the blood vessels. This finding is of importance because of the clinical similarities between (ME)CFS and sarcoidosis.*** *Shared symptoms include fatigue, neurologic dysfunction and arthralgia.* ***In patients with an elevated ACE level, attention to the lymph nodes and eyes is called for".*** Bell concluded: ***"The symptoms of (ME)CFS have long been viewed as a neurologic pattern, as indicated by other names for the condition such as myalgic encephalomyelitis (and) atypical poliomyelitis. Neurologic involvement is beginning to be confirmed by documentation of abnormalities in cerebral perfusion, hypothalamic function, and neurotransmitter regulation. A link is being forged between the symptoms pattern and objective evidence of CNS dysfunction.*** *A majority, and*

perhaps all, of the symptoms of (ME)CFS may be neurologic in origin. ***The view that (ME)CFS is a primary emotional illness has been undermined by research findings****"* (David S Bell. Postgraduate Medicine 1994:96:6:73-81).

1994

"Because a complete neurological examination is not emphasised as part of the diagnostic workup, it is possible that less obvious neurological findings may be overlooked. Careful evaluation of neurological features may be one approach to distinguishing subtypes*. The neurological symptoms and signs were neuropsychological changes, cutaneous sensory changes, paresis, abnormal muscle movements, abnormal muscle tone, deep tendon reflex changes, cranial nerve signs, posterior column signs, ataxia, and vasomotor instability.* ***Activity or exercise was a precipitant or exacerbation or relapse. Many of the neurological signs and symptoms were not reported on. A complete neurological examination should be an integral part of the diagnostic assessment of illnesses described as CFS"*** (NC Briggs, Paul Levine. Clin Inf Dis 1994:18: (Suppl 1):S32 –S42).

1995

To assess the clinical impression that patients with (ME)CFS do not walk normally, the gait kinematics of patients with (ME)CFS were studied. Results showed that (ME)CFS patients were significantly slower at running speed than the controls. Further analysis revealed that patients with (ME)CFS took smaller steps than the controls. *"****The data indicate that (ME)CFS patients have gait abnormalities when compared to sedentary controls. These could be due to balance problems, muscle weakness, or central nervous system dysfunction****"* (Boda WL, Natelson BH et al. Journal of the Neurological Sciences 1995:156-161).

1996

"A growing literature exists suggesting that a component of (ME)CFS may include abnormalities in cardiovascular control*. Vagal power, a measure of cardiac parasympathetic activity, was computed.* ***In an earlier study, we showed that patients with (ME)CFS had significantly less vagal power than healthy controls during controlled breathing. Our findings suggest that vagal dysregulation may be an additional symptom of (ME)CFS. Moreover, they suggest the presence of a biological link between fatigue and the autonomic nervous system. The (ME)CFS group had less vagal power than the controls at every stage (and also) during the first stage of recovery. These results indicate that vagal power responses in patients with (ME)CFS are different from healthy controls. A common complaint in (ME)CFS is that patients are unable to exert themselves for prolonged periods due to a lack of energy. Our findings might explain this. It is possible that reduced vagal power might interfere with the normal recovery process that follows bouts of exertion. This interference might exacerbate fatigue immediately or for several days following exertion, a common complaint in (ME)CFS. Decreases in vagal power have been identified in several medical conditions, including congestive heart failure. Our data suggest that (ME)CFS may involve a primary neurological abnormality. (ME)CFS patients also show dysfunction in complex auditory processing that is of the same magnitude as that found in patients with multiple sclerosis. Other data show that patients with ME/CFS*** *(sic)* ***had significantly lower brain stem perfusion ratios than either healthy or depressed controls"*** (DL Cordero, BH Natelson et al. Clinical Autonomic Research 1996:6:329-333).

1997

"The aim of this study was to investigate the role of the autonomic nervous system in (ME)CFS. Autonomic signs and symptoms have appeared frequently in reports of CFS, also called myalgic encephalomyelitis*. The three criteria used to determine autonomic symptoms eligibility were (1) dizziness upon standing and rapid heart beat; (2) dizziness upon standing and either nausea, diarrhoea, constipation and night sweats and (3) rapid heart beat and either nausea, diarrhoea, constipation or night sweats.* ***Recent reports have documented neurocardiogenic syncope in patients, again suggesting autonomic dysfunction in (ME)CFS. Several autonomic function test results were significantly different in the (ME)CFS group when compared to***

controls. Our study found that neither depression nor anxiety correlated with any of the measures of autonomic dysfunction. Deconditioning alone did not explain these autonomic abnormalities. 89% of patients in this study reported that the onset of fatigue was preceded by (an infectious illness), a history typical of patients with (ME)CFS. Our results provide evidence for an association between an autonomic neuropathy and (ME)CFS. An exercise programme, alone and in combination, cannot now be generally recommended for patients with (ME)CFS" (R Freeman, AL Komaroff. Am J Med 1997:102:357-364).

1998

"Spatial and temporal parameters of gait were collected from (ME)CFS patients by using instrumentation of movement analysis. ***Interestingly, abnormalities were present from the beginning of the gait, which indicates that they are unlikely to be caused by the rapidly increasing fatigue. This strengthens the hypothesis of a direct involvement of the central nervous system in the onset of the disease****"* (R Saggini et al. Journal of the Neurological Sciences 1998:154:18-25).

1998

"A substantial body of clinical evidence now supports an association between various forms of hypotension and (ME)CFS. Features that exacerbated (patients') fatigue included physical exertion, a hot shower, prolonged standing (such as waiting in line at the grocery store) and a warm environment. Importantly, all (ME)CFS patients but none of the controls developed orthostatic symptoms (during testing), suggesting that orthostatic intolerance may be a defining feature of the illness. Virtually all (ME)CFS patients have their symptoms provoked by the simple process of assuming an upright posture. There is a high prevalence of allergic disease among those with (ME)CFS *(and) one would expect to find a mechanism by which allergic disease increases the activation of the NMH reflex pathway. Undem et al have shown that both viral infection and allergic reactions to food antigens enhance the excitability of mechanically sensitive vagal afferents in the airway (which provides a link between these clinical situations).* ***Investigations into the high prevalence of neurally mediated hypotension and other forms of autonomic dysfunction among those with (ME)CFS should improve our understanding of this disorder****"* (Peter C Rowe and Hugh Calkins. Am J Med 1998:105:3A:15S-21S).

1999

"The fatigue in (ME)CFS is similar to that found in disorders of the central nervous system such as multiple sclerosis, Parkinson's disease and multiple system atrophy*. It is now clear that (ME)CFS patients differ from patients with major depression in their symptoms (and) biologic markers such as steroid metabolism. We propose dysfunctional ion channels in the cell membranes as the key abnormality in (ME)CFS which may also be responsible for the altered neuroendocrine functions reported in this condition. Associated symptoms that are common in (ME)CFS include paroxysmal attacks of angina-like chest pain (Syndrome X), nocturnal attacks of sweating and palpitations, irritable bowel syndrome, vertigo or dysequilibrium, photophobia (and) daily migraine-like headaches. Autonomic dysfunction in (ME)CFS is well-recognised.* ***One of the most characteristic features of the illness is the fluctuation in symptoms which can be induced by physical and/or mental stress****. Acquired ion channel abnormalities in myocardium could explain the pathogenesis of Syndrome X. Acquired mutations of a similar nature may form the basis of the cardiac dysfunction seen in Syndrome X and (ME)CFS. The role of abnormal ionophores governing both Syndrome X and (ME)CFS assume importance in the light of the fact that a highly significant proportion of (ME)CFS patients have cardiomyopathy. (ME)CFS is an episodic neurological disorder with a basic mechanism of disease involving abnormal ion channel functions"* (Abhijit Chaudhuri et al. Hum Psychopharmacol Clin Exp 1999:14:7-17).

2000

In 2000, the CFIDS Association of America produced a 24 page document entitled "**Neurological Findings in (ME)CFS: A Survey of the Research"** containing 175 references. It is available from the CFIDS Association of America, email: info@cfids.org

2001

A quantitative assessment of cerebral ventricular volumes in (ME)CFS patients found that volumes were larger than in the control groups. "*The results of this study provide further evidence of pathophysiological changes in the brains of participants with (ME)CFS"* (Lange G, Natelson BH et al. Appl Neuropsychol 2001:8(1):23-30).

2003

Byron Hyde, medical adviser on ME/CFS to the Canadian Government, pointed out that "***ME in adults is associated with measurable changes in the central nervous system and autonomic function and injury to the cardiovascular, endocrine and other organs and systems. The patient with the diagnosis of ME/CFS is chronically and potentially seriously ill. These ME/CFS patients require a total investigation and essentially a total body mapping to understand the pathophysiology of their illness and to discover what other physicians may have missed. A patient with ME is a patient whose primary disease is central nervous system change, and this is measurable. The belief that ME/CFS is a psychological illness is the error of our time".*** (The Complexities of Diagnosis. Byron Hyde. In: Handbook of Chronic Fatigue Syndrome Leonard A Jason et al. John Wiley & Sons, Inc. 2003).

2003

Research at the Salk Institute, La Jolla, California, identified a gene that may link certain pesticides and chemical weaponry to a number of neurological disorders. The finding, published in the 17 March online version of Nature Genetics, was the first to demonstrate a clear genetic link between neurological disorders and exposure to organophosphate (OP) chemicals. OPs include household pesticides as well as the nerve gas sarin. The research showed that OPs inhibit the activity of a gene called neuropathy target esterase (NTE). Some of the neurological problems echoed many of the symptoms of Gulf War Syndrome.

This is important because the Proceedings of The National Academy of Science (PNAS) published evidence that NTE is inhibited by several OP pesticides, chemical warfare agents, lubricants and plasticisers, leading to OP-induced delayed neuropathy in more than 30,000 human cases (PNAS 2003:100:13:7983-7987).

(This is highly significant in ME/CFS, because subsequent gene expression research demonstrated 16 genes as having an expression profile associated with (ME)CFS. These genes can be grouped according to immune, neuronal and mitochondrial functions. A neuronal component was identified that is associated with central nervous system hypomyelination, and the researchers specifically noted the association of organophosphates and chemical warfare agents: *"A neuronal component is suggested by up-regulation of NTE. NTE is a target for organophosphates and chemical warfare agents, both of which may precipitate (ME)CFS"* (N Kaushik, ST Holgate, JR Kerr et al. J Clin Pathol 2005:58:826-832). Stephen Holgate is MRC Clinical Professor of Immunopharmacology at the University of Southampton and this is top-rank research, not mere hypothesis).

2004

"The purpose of this study was to determine whether brain activity of (ME)CFS patients during voluntary motor actions differs from that of healthy controls*. Fifty-eight channels of surface EEG were recorded simultaneously from the scalp. Major findings include (1) Motor performance of the (ME)CFS patients was poorer than the controls (2) Relative power of EEG theta frequency band during performance of tasks was significantly*

greater in (ME)CFS than in the control group (3) The amplitude of MRCP (motor activity-related cortical potential) negative potential for tasks was higher in (ME)CFS than the control group. ***These results clearly show that (ME)CFS involves altered central nervous system signals in controlling voluntary muscle activities, especially when the activities induce fatigue. Physical activity-induced EEG signal changes may serve as physiological markers for more objective diagnosis of (ME)CFS***" (Siemionow V et al. Clin Neurophysiol 2004:115(10:2372-2381).

2004

The Lancet published a Review entitled "**Fatigue in neurological disorders**" by Abhijit Chaudhuri et al (Lancet 2004:363:978-988). It included (ME)CFS as a neurological disease and it contained 94 references.

2005

In a study looking at grey matter volume reduction in (ME)CFS, researchers found significant reductions in global grey matter volume in (ME)CFS patients compared with matched controls: "*Moreover, the decline in gray matter volume was linked to the reduction in physical activity, a core aspect of (ME)CFS. These findings suggest that the central nervous system plays a key role in the pathophysiology of (ME)CFS and point to an objective and quantitative tool for clinical diagnosis of this disabling disorder"* (FP de Langea et al. NeuroImage 2005:26:3:777-781).

2005

A News Release from Georgetown University Medical Centre highlighted objective, physiological evidence that (ME)CFS ***"can be considered a legitimate medical condition.*** *James Baraniuk, Assistant Professor of Medicine (said) 'Our research provides initial evidence that that (ME)CFS and its family of illnesses may be legitimate neurological diseases and that* ***at least part of the pathology involves the central nervous system'*** *".* The researchers stated: "*CFS, Persian Gulf War Illness and fibromyalgia are overlapping symptom complexes.* ***Neurological dysfunction is common****. We assessed cerebrospinal fluid to find proteins that were differentially expressed in this CFS-spectrum of illnesses compared to controls. Pooled CFS and (Gulf War Syndrome) samples shared 20 proteins that were not detectable in the control sample. 62 of 115 proteins were newly described. This pilot study detected an identical set of central nervous system, innate immune and amyloidogenic proteins in the cerebrospinal fluids from two independent cohorts of subjects with overlapping (ME)CFS, (Gulf War Syndrome) and fibromyalgia"* (BMC Neurology 2005:5:22).

2007

Professor Julia Newton et al studied the prevalence of autonomic dysfunction in (ME)CFS; she found that symptoms of autonomic dysfunction were strongly and reproducibly associated with the presence of (ME)CFS and correlated with severity of fatigue. A particularly strong association was seen with symptoms of orthostatic intolerance, suggesting that abnormality of dynamic blood pressure regulation is particularly associated with fatigue severity in ME/CFS, confirming the conclusions of a previous review, and it made clear that ME/CFS patients are not deconditioned (Q J Med 2007:100:519-526).

2008

Hoad A and Newton J et al described the prevalence of POTS (postural orthostatic tachycardia syndrome) in a cohort of patients with ME/CFS and suggest that prevalence may be even higher than shown in the study results because observations of haemodynamics were limited to just two minutes (some patients were unable to stand without support and were too unwell to be tested). The authors state: "*Studies suggest that POTS is accompanied with a range of autonomic nervous system abnormalities including vagal withdrawal and enhanced sympathetic modulation, associated with findings consistent with pooling in the lower limbs. It is important that (in ME/CFS patients) appropriate investigations are performed. We suggest that at the very minimum this*

includes haemodynamic assessment in response to standing of patients attending CFS/ME clinical services" (Q J Med September 2008:doi:10.1093/qjmed/hcn123).

2009

Newton et al demonstrated that lower blood pressure and abnormal diurnal blood pressure regulation occur in patients with ME/CFS and considered the links between hypotention and fatigue. The authors concluded: *"Compared with the control population, the (ME)CFS group had significantly lower systolic blood pressure and mean arterial blood pressure and exaggerated diurnal variation. There was a signficant inverse relationship between increasing fatigue and diurnal variation of blood pressure in the (ME)CFS group. This study has further consolidated the evidence that lower blood pressure occurs in (ME)CFS and that…lower night-time blood pressure seems to be a significant problem that may lead to enhanced diurnal variation in blood pressure that associates with fatigue. We and others have previously demonstrated that autonomic nervous system function is significantly impaired in (ME)CFS. We would suggest that…one mechanism whereby abnormalities in autonomic function may be manifest clinically is through blood pressure dysregulation"* (Psychsom Med 2009:71: doi:10.1097/PSY.0b013e31819ccd2a).

Documented abnormalities shown on neuroimaging in ME/CFS

As reported by Dr John Breward as long ago as 2001 in the Newsletter of The 25% ME Group, Issue 11: ***"The cumulative evidence is now incontestable: there are measurable physical abnormalities in the brain in ME"***.

1992

"(ME)CFS is a severely disabling illness. Compared to the normal control group, the (ME)CFS group showed significantly lower cortical / cerebellar rCBF (regional cerebral blood flow) ratios throughout multiple brain regions. SPECT provided objective evidence for functional impairment of the brain in the majority of the (ME)CFS subjects. The central nervous system dysfunction in (ME)CFS may be a primary phenomenon or it may be secondary to undefined systemic factors. The majority of (ME)CFS subjects studied showed SPECT scan abnormalities providing objective evidence of central nervous system dysfunction in (ME)CFS" (M Ichise et al; Nuclear Medicine Communications 1992:13:767-772).

1994

"We compared SPECT scans of patients with (ME)CFS with those of patients with ADC (AIDS dementia complex) and unipolar depression. The MCUI (midcerebral uptake index) was signficantly different across all groups. This study demonstrates that (ME)CFS shares some similarities on SPECT imaging with both ADC and unipolar depression. The MCUI was significantly lower in patients with (ME)CFS and ADC than in patients with major unipolar depression or the healthy comparison group. By this objective standard, the pathophysiologic process in the central nervous system of patients with (ME)CFS would seem to be more similar to that in patients with ADC than to patients with unipolar depression. Moreover the MCUI values correlated with the regional defect count in the (ME)CFS and ADC groups, but not in the depressed patients or control subjects" (Schwartz RB et al; American Journal of Reontgenology 1994:162:943-951).

1995

"We looked for brain perfusion abnormalities in patients with ME/CFS. Hypoperfusion of the brainstem was marked and constant. Brainstem hypoperfusion was confirmed in all ME/CFS patients. Patients with ME/CFS have a generalised reduction of brain perfusion, with a particular pattern of hypoperfusion of the brainstem. Brainstem hypoperfusion appears to be the differentiating factor between our ME/CFS patients and those with major depression.

The hypothalamus of ME/CFS patients shows functional abnormalities different from those in depressed patients. Our data suggest that brainstem hypoperfusion in ME/CFS patients could be due to an organic abnormality" (DC Costa et al; Q J Med 1995:88:767-773).

1995

"Many neurological diseases produce symptoms of intense fatigue and muscle pain. Abnormalities in cerebral perfusion were seen on visual reporting of the SPECT images in more than half of the patients with (ME)CFS. Perfusion defects were not consistently localised to any one region of the brain, being found in the frontal, temporal, occipital and parietal regions, nor were the defects always unilateral. (ME)CFS is an established, severe and debilitating illness. We have found visual evidence of cerebral perfusion defects in all regions of the brain. This is confirmed by the objective quantitative analysis which demonstrates that there is a greater variability in perfusion pattern of patients with (ME)CFS compared to normal subjects" (J Patterson et al; EOS- J Immunol Immunopharmacol 1995:XV:1-2:53-58).

1998

D Di Giuda, G Racciatti et al found that ***"(ME)CFS is a severely disabling illness. Regional brain perfusion impairment (mainly hypoperfusion) was found in 83.9% of (ME)CFS patients. This study confirmed previous reports of brain perfusion impairment in (ME)CFS, providing objective evidence of central nervous system dysfunction".*** ("Brain SPET in Chronic Fatigue Syndrome": Fourth AACFS International Research & Clinical Conference, Mass: USA).

2001

Cook DB, Natelson BH et al from the Department of Neurosciences, New Jersey Medical School, reported: "*Some have suggested that (ME)CFS is a 'functional somatic syndrome' in which symptoms are inappropriately attributed to a serious illness. However, brain magnetic resonance imaging (MRI) data suggest that there may be an organic abnormality associated with (ME)CFS. (Our) results demonstrate that the presence of brain abnormalities in (ME)CFS are significantly related to subjective reports of physical function and that (ME)CFS subjects with MRI brain abnormalities report being more physically impaired than those without brain abnormalities"* (Int J Neurosci 2001:107(1-2):1-6).

2002

A study by Puri et al tested the hypothesis that (ME)CFS is associated with altered cerebral metabolite in the frontal and occipital cortices and concluded: "*Our results suggest that there may be an abnormality of phospholipid metabolism in the brain in (ME)CFS"* (Acta Psychiatr Scand 2002:106(3):224-226). As Dr Charles Shepherd, Medical Advisor to the ME Association, commented: "*These results add further weight to recently reported perfusion studies which suggest that there may be pathophysiological abnormalities in the cerebral cortex of ME/CFS patients"* (Co-Cure MED: 30th August 2002).

2002

Researchers in Japan (Kuratsune et al) reported that their findings "*suggest that the levels of biosynthesis of neurotransmitters through acetylcarnitine might be reduced in some brain regions of (ME)CFS patients"* (NeuroImage 2002:17(3):1256-1265).

2003

Using proton magnetic resonance spectroscopy to study the metabolic functions of the basal ganglia in (ME)CFS patients, Chaudhuri et al reported: "*A highly significant increase in the spectra from choline-containing compounds was seen in the (ME)CFS patient group"* (Neuroreport 2003:14(2):225-228).

2003

German researchers Siessmeier et al used 18-fluorodeoxyglucose positron emission tomography (FDG-PET) to evaluate cerebral glucose metabolism in (ME)CFS and concluded: "*PET may provide valuable information in helping to separate CFS patients into subpopulations with and without apparent alterations in the central nervous system"* (JNNP 2003:74(7):922-928).

2005

Lange and Natelson et al from New Jersey Medical School studied attentional processes (cognitive difficulties) in patients with (ME)CFS: *"Our results provide objective evidence in support of the subjective report of cognitive difficulties in individuals with (ME)CFS and demonstrate an important role for functional neuroimaging in understanding the pathophysiology of (ME)CFS symptoms. The evidence supporting a central nervous system pathophysiological process for some individuals with (ME)CFS is mounting. Findings showed that individuals with (ME)CFS utilise more extensive (brain) regions. Individuals with (ME)CFS appear to have to exert greater effort to process auditory information as effectively as similar healthy adults. Our studies do not support the notion that difficulties in cognitive function in individuals with (ME)CFS are related to poor motivation"* (NeuroImage 2005:26(2):513-524).

2007

Further to their 2005 study, DB Cook et al from New Jersey Medical School used functional MRI (fMRI) to determine the association between feelings of mental fatigue and blood oxygen level dependent (BOLD) brain responses during a mentally fatiguing cognitive task in (ME)CFS patients. "*Our results demonstrated significant associations between mental fatigue and brain activity during a fatiguing cognitive task (and are) generally consistent with prior research. Brain regions that were significantly related to mental fatigue included the parietal, cingulated, inferior frontal and superior temporal cortices, cerebellum and cerebellar vermis – regions that have been demonstrated as important for several aspects of cognitive function. Chronically fatigued participants exhibited greater brain activity in multiple brain regions during the fatiguing task compared to controls. The results suggest that the phenomenon of mental fatigue can exert demands on the neural processes necessary for efficient information processing"* (NeuroImage 2007: doi:10.1016/j.neuroimage.2007.02.033).

2008

In this paper, Japanese researchers summarised neuroimaging findings in patients with (ME)CFS from 1992, including reduced brain blood flow, decreased brain volume and symptom-related neuroimaging changes. They reported: "*An increasing amount of neuroimaging evidence supports the hypothesis that (ME)CFS patients have structural or functional abnormalities within the brain. Available neuroimaging data not only show differences between fatigued patients and normal controls, but also indicate the brain's response to mental fatigue and other complex symptoms of (ME)CFS. Evidence of abnormal perfusion has led to research on brain metabolism (that) found significant hypometabolism in the right mediofrontal cortex and brainstem in (ME)CFS patients. Patients with (ME)CFS have been found to have significantly abnormal brain volume compared with healthy controls and these abnormalities occur not only in white matter but also in grey matter. It is well known that cytokines produced in the brain exert various central actions, including activation of the sympathetic nervous system and HPA axis, impairment of learning memory etc; this points to the possibility that brain cytokines may play a role in the pathogenesis of (ME)CFS.* ***We suggest that the focal point of (ME)CFS research should be transferred to the central nervous system****"* (J Int Med Res 2008:36:867-874).

Given the now-substantial evidence of abnormalities in ME/CFS patients which have been demonstrated on neuroimaging, it is disturbing that the Wessely School apparently continues to dismiss them as of no consequence. Wessely's colleague at the IoP, Anthony David, long ago went on record as being dismissive of neuroimaging in ME/CFS, asserting that the clinical significance of such testing *"has yet to be determined"* (Helen Cope, Anthony David et al; Br J. Psychiat 1995:167:86-94) and that *"It is premature …to claim unique*

neuroimaging abnormalities in the chronic fatigue syndrome" (JNNP 1996:60:471-473), a dismissive stance further propounded by the Wessely School's Joint Royal Colleges' Report on CFS (CR54; 1996) which was categoric that neuroimaging "*may reveal 'abnormalities' of little consequence (whose) significance remains to be determined"*.

This advice has seemingly ensured that, for non-private patients in the UK, it is virtually impossible for people with ME/CFS to be referred for neuroimaging.

Documented neuroendocrine abnormalities

1991

"Several lines of evidence suggest that the various components of the hypothalamic-pituitary-adrenal (HPA) axis merit further study in these patients. Debilitating fatigue, an abrupt onset precipitated by a stressor, feverishness, arthralgias, myalgias, adenopathy, postexertional fatigue, exacerbation of allergic responses are all characteristic of glucocorticoid insufficiency. ***Compared to controls, patients with (ME)CFS showed a significant reduction in basal total plasma cortisol (and) a proportionately higher response to the amount of ACTH released during stimulation with oCRH. We suggest that the hyper-responsiveness of the adrenal cortex to ACTH in patients with (ME)CFS reflects a secondary adrenal insufficiency in which adrenal receptors have become hyper-responsive to inadequate levels of ACTH. In the light of the post-infectious presentation of (ME)CFS in the majority of patients, it should be noted that viral infections can alter neurotransmitter and / or neuroendocrine regulation"*** (Mark A Demitrack et al. Journal of Clinical Endocrinology and Metabolism 1991:73:6:1224-1234).

1992

"The syndrome of (ME)CFS has a lengthy history in the medical literature. The clinical presentation, with evidence of persistent immune stimulation, lends support to the idea that (ME)CFS represents a clinical entity with potential biological specificity. ***We showed that patients with (ME)CFS demonstrate a significant hypocortisolism****"* (Mark A Demitrack et al. Biol Psychiatry 1992:32:1065-1077).

1993

"Patients with (ME)CFS lose muscle protein synthetic potential, but not muscle bulk. These perturbations may contribute to the feature of muscle weakness associated with persistent viral infection in the muscles themselves. 80% of patients had serological indications of current or on-going VP1 positive enterovirus infection*. There has to be persistent enterovirus infection to produce the response; it does not rely on the body's development of antibody.* ***Furthermore, skeletal muscle RNA was significantly reduced. This reflects a reduced capacity to synthesise proteins. Our results imply that there is a subgroup of patients with (ME)CFS in which symptoms of skeletal muscle weakness may be related to proximal myopathy. Direct evidence has been obtained for a subcellular metabolic defect in the muscle per se. These studies indicate that up to 80% of patients with (ME)CFS have identifiable mitochondrial abnormalities"*** (VR Preedy TJ Peters et al. J Clin Pathol 1993:46:722-726).

1993

"The baseline AVP values were significantly lower in patients with (ME)CFS when compared to healthy controls. The mean total body potassium (TBK) was 9% lower than predicted*. This study also showed that some patients with (ME)CFS appear to have an increased total body water content when compared with healthy controls. Abnormalities of water metabolism in patients with (ME)CFS have previously been reported.* ***This interference with hypothalamic function may be due to the presence of persistent virus, most likely enterovirus. In such a chronic infection, Oldstone has shown that the agent may persist in cells without***

producing any evidence of damage but effecting a profound disturbance of hormones and neurotransmitters" (AMO Bakheit et al. Acta Neurol Scand 1993:87:234-238).

1994

"One of the characteristic complaints of patients with (ME)CFS is the skeletal muscle-related symptom. We show that patients had a deficiency of serum acylcarnitine. This deficiency might induce an energy deficit and/or abnormality of the intramitochondrial condition in the skeletal muscle, resulting in general fatigue, myalgia, muscle weakness and postexertional malaise in patients with (ME)CFS. The measurement of acylcarnitine would be a useful tool for the diagnosis and assessment of (ME)CFS" (H Kuratsune et al. Clin Inf Dis 1994:18: (Suppl 1):S62-S67).

1995

"The role of steroids in growth hormone production was determined in patients with (ME)CFS. There were abnormal responses of growth hormone production to administered steroids in patients with (ME)CFS. These data suggest an abnormality in the glucocorticoid receptor bearing neurones that control growth hormone responses in affected patients. These data clearly pointed to an abnormality in neuroendocrine control. Another condition that bears striking similarities to (ME)CFS is post-polio syndrome" (T Majeed et al. Journal of the Irish Colleges of Physicians and Surgeons 1995:24:1:20-24).

1996

In a study examining abnormality of adrenal function, Japanese researchers found that *"**these abnormalities are quite different from those found in patients with mental or physical diseases reported previously**"* (Yamaguti K et al. JCFS 1996:2:2/3:124-125).

1996

"In reviewing stress-response systems, it is important to keep in mind that activity of stress-response systems is determined by genetic and environmental factors. ***In (ME)CFS we have demonstrated a significant increase in plasma levels of the serotonin metabolite 5-hydroxyindoleacetic acid. Patients with a longer duration of disease do tend to have more severe basal abnormalities in cortisol levels***" (LJ Crofford et al. Rheum Dis Clin N Am 1996:22:2:267-284).

1996

"There is an increasing volume of evidence to support the view that patients with (ME)CFS have unique endocrinology patterns. The cardinal findings include attenuated ACTH responses to CRH and low 24-hour urinary cortisol. These are compatible with a mild central adrenal insufficiency. It is well-documented that infectious diseases are often accompanied by various forms of neuroendocrine disturbances with acute viral infections activating the HPA axis. An increase in peripheral turnover of 5-HT may explain the heightened allergic responsiveness as well as the musculoskeletal pain seen in (ME)CFS" (LV Scott TG Dinan. JCFS 1996:2:4:49-59).

1997

"It is notable that the pattern of alteration in the stress response suggests a sustained inactivation of central nervous system components of this system. ***It has not escaped the view of clinical authors that (ME)CFS and its historical antecedents shares many of the characteristics with endocrine disease states (in which there is) functional interdependence of the endocrine system and the nervous system****. It is only recently that clinical researchers have clearly documented that neuroendocrine disturbances are evident in patients with (ME)CFS (which) have brought into view a broader understanding of the variety of physiologic accompaniments of this condition.*

(ME)CFS appears to wax and wane with periods of increased stress. ***Results of this work provide confirmatory support for an impairment (of) the HPA axis (and) is consistent with the view that adrenocortical function is impaired****"* (MA Demitrack. J psychiat Res 1997:31:1:69-82).

1998

"Our group has established that impaired activation of the HPA axis is an essential neuroendocrine feature of (ME)CFS. *It is now recognised that (ME)CFS leads to significant physical and psychological debility in a large segment of the population. We have suggested that the findings of reduced adrenal glucocorticoid function in (ME)CFS are most consistent with a central nervous system defect in the activation of this axis.* ***(We found) a basal hypocortisolism. On its own, this observation is a striking finding. These observations provide an important clue to the development of more effective treatment for this disabling condition****"* (MA Demitrack, LJ Crofford. Ann N.Y. Acad Sci 1998:840:684-697).

1999

"The right and left adrenal gland bodies were reduced by over 50% in the (ME)CFS subjects, indicative of significant adrenal atrophy in a group of (ME)CFS with abnormal endocrine parameters*"* (Scott LV et al. Psychoneuroendocrinology 1999:24:7:759-768).

2000

*"****Baseline adrenaline levels were significantly higher in (ME)CFS patients. We conclude that (ME)CFS is accompanied by a resistance of the immune system to regulation by the neuroendocrine system. Based on these data, we suggest (ME)CFS should be viewed as a disease of deficient neuroendocrine-immune communication****"* (Kavelaars A et al. J Clin Endocrinol Metab 2000:85:2:692-696).

2001

"In the investigation of (ME)CFS, fine needle aspiration (FNA) cytology has been tested in addition to conventional biochemical thyroid function tests. Of 219 patients, 40% were diagnosed with definite cytological lymphocytic thyroiditis. ***We strongly advocate FNA cytologic assessment of the thyroid in patients with (ME)CFS****"* (B Wikland et al. Lancet 2001:357:956-957).

In a subsequent letter, Wikland stated: "*In a letter published in The Lancet (24th March 2001) we report on fine needle aspiration cytology of the thyroid in (ME)CFS. No less than 40% of our patients showed definite autoimmune thyroiditis. Less than half of these patients fulfilled conventional biochemical criteria of hypothyroidism.* ***In our opinion, this aspect merits wider recognition****"* (Bo Wikland. eBMJ 9 January 2002).

2001

"One of the most consistent findings in (ME)CFS is a decrease in Th1-mediated immune responses. (ME)CFS patients have been shown to display a disturbed HPA axis and have low levels of cortisol. We speculate that in these patients IL-10 and IL-12 are differently affected by glucocorticoids. ***The present study shows that, in particular, IL-10 secretion (and its sensitivity to GC) differs from that in healthy controls****"* (J Visser et al. Journal of Neuroimmunology 2001:119:2:343-349).

2003

"Endocrinologists were not included in the working groups that prepared two recent reports on (ME)CFS, despite its clinical overlap with Addison's disease, which is a classic endocrine disease. The failure to include at least one endocrinologist in those panels may explain why in their reports there is not a single word about the 42 clinical features that (ME)CFS shares with Addison's disease*.*** *The failure of both the*

English and Australian reports to mention other important endocrine abnormalities of (ME)CFS represents a serious omission. Cognitive behaviour therapy may have benefited depressed subjects (but) not patients with (ME)CFS. ***(ME)CFS and Addison's disease also share reduced cardiac dimensions, increased heart rate, postural hypotension, orthostatic tachycardia, dizziness upon standing, dehydration, anorexia, nausea (and) diarrhoea. Moreover (they) also share leucocytosis, lymphocytosis, elevations of transaminase values, enhanced TSH secretion, respiratory muscle dysfunction, reduction in exercise capacity and increased sensitivity to chemical exposures****. Reason suggests that the clinical overlap of (ME)CFS with Addison's disease reflects the endocrine and adrenal abnormalities found in (both disorders) and omitted unjustifiably in both the English and Australian reports, namely hypocortisolism, impaired adrenal cortical function, reduced adrenal gland size, antibodies against the adrenal gland, and impaired production of DHEA.* ***Richard Horton, editor of The Lancet, has recently written*** *(JAMA 2002:287:2843-2847)****: 'Failure to recognise the critical footprint of primary research weakens the validity of guidelines and distorts clinical knowledge****' "* (R Baschetti. Eur J Clin Invest 2003:33:1029-1031).

(Baschetti was referring to the 2002 UK Report of the CMO's Working Group and the Australian Report in the Medical Journal of Australia 2002:176:S17-S56).

2003

"Patients with (ME)CFS typically present a normal thyroid function. From (our) observations, we raise the hypothesis that molecular mechanisms could explain the development of a clinical hypothyroid state in the presence of a normal thyroid function. Whilst biochemically euthyroid, (ME)CFS patients are clinically hypothyroid. Signal transduction mechanisms could account for a peripheral T3 resistance syndrome leading to a clinically hypothyroid but biochemically euthyroid state, as observed in diseases characterised by dysregulations in the antiviral pathway or during the therapeutic use of INF α / β" (P Englebienne et al. Med Hypotheses 2003:60:2:175-180).

2003

The following article is in Serbian and comes from the Institute of Endocrinology, Belgrade; no author is listed:

"Similarities between the signs and symptoms of (ME)CFS and adrenal insufficiency prompted the research of the HPA axis derangement in the pathogenesis of (ME)CFS. ***We compared cortisol response in the (ME)CFS subjects with the response in control subjects and in those with secondary adrenal insufficiency. We have shown that cortisol increment at 15 and 30 minutes is significantly lower in the (ME)CFS group than in controls. However, there was no difference between the (ME)CFS group and those with secondary adrenal insufficiency in any of the parameters. Consequently, reduced adrenal responsiveness to ACTH exists in (ME)CFS****"* (Srp Arh Celok Lek 2003:131:9-10:370374).

It should be noted that Wessely School psychiatrists have carried out several endocrinological studies on "CFS" patients and have had varying results, possibly because of their chosen case definition. Despite the compelling evidence of international researchers, the Wessely School psychiatrists found no evidence of endocrine abnormality in some of their studies, whilst in others they did find evidence of such abnormalities but concluded that even though a distinct abnormality was found (low cortisol), it was likely to be *"an epiphenomenon caused by the behavioural changes typical of CFS"* (GJ Rubin, M Hotopf, A Cleare et al. Psychosom Med 2005:67:3:490-499).

Documented evidence of inflammation in ME/CFS

A few illustrations of published evidence of inflammation of the central nervous system of ME/CFS patients include the following:

1955

In this outbreak of ME in Adelaide, Australia, an agent was repeatedly transmitted to monkeys; when the monkeys were killed, microscopically, infiltration of nerve roots with lymphocytes and mononuclear cells was seen and some of the nerve fibres showed patchy damage in the myelin sheaths and axon swellings consistent with neurological involvement. In these monkeys, there were widespread changes involving the **dorsal root ganglia**, cervical and lumbar nerve roots and peripheral nerves. Perivascular collars of lymphocytes and plasma cells were in the cerebral cortex, brainstem and cerebellum, spinal cord and around blood vessels to nerve roots (Pellew RAA, Miles JAR; Med J Aust:1955:2:13:480-482, cited by J Gordon Parish; Postgraduate Medical Journal 1978:54:711-717).

This is particularly significant, given the recent autopsy evidence presented at the Royal Society of Medicine meeting in the series "Medicine and me" on 11th July 2009 by Dr Abhijit Chaudhuri, where he showed slides of inflammation of the dorsal root ganglia in three ME/CFS patients.

1970

Innes reported isolation of Coxsackie B2 virus from the cerebrospinal fluid: *"The isolation of an enterovirus from the cerebrospinal fluid in the fourth month is in itself remarkable"* (Innes SGB; Lancet:1970:969-971).

1992

"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****"* (Buchwald, Cheney, Peterson D, Komaroff, Gallo et al; Ann Int Med: 1992:116:103-113).

1994

*"****As with any chronic inflammatory condition affecting the central nervous system****, the T2-bright foci on MRI in (ME)CFS may represent a perivascular cellular infiltrate and/or reactive demyelination of the surrounding white matter. Alternatively, these abnormalities may reflect the results of a vasculopathy specifically involving the small vessels of the cerebral white matter. Specifically, on the basis of our observations, the white matter abnormalities seen on MRI images may represent foci of gliosis or chronic demyelination, which appear to be irreversible"* (Schwartz RE et al; Am J Roentgenology:1994:162:935-941).

1997

"It is now evident that this illness is not simply an imaginary one, nor the result of anxiously amplifying normal bodily sensations. Substantial objective evidence of abnormalities in the central nervous system is now available. Magnetic resonance imaging has revealed punctate areas of high signal in the white matter more often in patients with (ME)CFS than in healthy controls. They may represent areas of ***inflammation*** *or demyelination"* (Komaroff AL (JAMA:1997:278:14:1179-1184).

2004

"These findings are consistent with an activated inflammatory response*. Shockingly, the mean QOL (quality of life) scores as regards limitations on physical functioning were very, very low, similar to those found in people with AIDS and multiple sclerosis*" (Advances in biomedical understanding of ME. Neil Abbot. Vance Spence. InterAction May 2004).

2006

"(ME)CFS is a poorly defined medical condition which involves inflammatory and immune activation*. The Type I interferon antiviral pathway has been repeatedly shown to be activated in the most afflicted patients. An abnormal truncated form of ribonuclease L (37-kDa RNase L) is also found in (ME)CFS patients and this protein has been proposed as a biological marker for (ME)CFS****. The levels of this abnormal protein have been significantly correlated to the extent of inflammatory symptoms displayed by (ME)CFS patients. (Our) results suggest that chronic inflammation due to excess nitric oxide plays a role in (ME)CFS and that the normal resolution of the inflammatory process is impaired****"* (M Fremont, K De Meirleir et al. JCFS 2006:13(4):17-28).

2007

"Our expanded understanding of the genomics of (ME)CFS has reinforced the evidence that the illness is rooted in a biologic pathogenesis that involves cellular dysfunction and interactions between the physiologic stress response and ***inflammation****. These patients displayed increased anti-inflammatory cytokines"* (Klimas NG et al; Curr Rheumatol Rep 2007:9:6:482-487).

2008

In a personal communication, Nancy Klimas, Professor of Medicine at the University of Miami, world-renowned immunologist and expert on ME/CFS, said that 80% of all ME/CFS patients (both severely and not so severely ill) do have evidence of inflammation if the correct scans are employed, and she believes that 100% of ME/CFS patients actually have inflammation.

2008

On 17th December 2008 Emory University School of Medicine issued a press release by Kathi Baker: "*A new study conducted by researchers from Emory University and the Centres for Disease Control and Prevention (CDC) shows that* ***individuals with (ME)CFS have increased blood levels of the inflammatory chemicals*** *known to increase risk for developing illnesses ranging from cardiovascular disease and dementia to diabetes and cancer. 'We don't know where the increased inflammation is coming from in patients with (ME)CFS symptoms in our study, and although depression has been associated with increased inflammation, in our study it did not account for the increased inflammation in individuals with (ME)CFS' (explained Dr Charles L Raison). The researchers found that subjects with (ME)CFS had higher levels of CRP (c-reactive protein) than did well individuals and also had higher scores on an inflammatory factor that included both CRP and white blood cell levels"*

2009

In the study to which the above press release relates, the authors stated: "*The current study examined plasma concentrations of high-sensitivity c-reactive protein (hs-CRP), white blood cell count (WBC) and a combined inflammation factor in a large (457) population-based sample. Log-transformed mean plasma concentrations of hs-CRP were increased in subjects with (ME)CFS when compared to subjects who were well"* (Charles L Raison et al; Brain, Behaviour and Immunity 2009:23:3:327-337).

2009

Professor M Maes from Belgium reviewed recent findings on inflammatory and oxidative and nitrosative stress pathways and reported: "***The 'psychosomatic' symptoms experienced by (ME/CFS patients are caused by intracellular inflammation.*** *Symptoms occurring in (ME)CFS have a genuine organic cause, that is activation of peripheral and central IO and NS pathways and gut-derived inflammation"* (Curr Opin Psychiatry 2009:22(1):75-83).

Note on inflammation

Following an international meeting on inflammation held in Bordeaux, France, Robert Dantzer et al published a Review entitled "Identification and treatment of symptoms associated with inflammation in medically ill patients" (Psychoneuroendocrinology 2008:33:18-29). Given the documented evidence of inflammation in ME/CFS, this Review has important implications for people with the disorder. It recommends testing with a standard battery of inflammatory markers in medically ill patients. Quotations that might be relevant for people with ME/CFS include the following:

"This meeting brought together clinicians and basic scientists with a common interest in understanding inflammation and associated symptoms in medically ill patients (and it) focused on: (a) predominant symptoms associated with inflammation, (b) markers of inflammation at the periphery, (c) possible markers of brain inflammation associated with low-grade peripheral inflammation in humans, (d) animal models of inflammation-associated symptoms, and (e) domains of intervention for controlling inflammation-associated symptoms".

"The diagnostic tools that are favoured by psychiatrists are clearly not the best ones. As pointed out by Joel Dimsdale (San Diego, CA), the concept of somatisation that is used for characterising symptoms in the absence of any detectable disease is of little operational value, if not misleading".

"For instance, the enduring fatigue experienced by the vast majority of breast cancer survivors could easily be labelled as somatisation disorder according to the 4th Edition of the Diagnostic and Statistical Manual of Mental Disorders".

"Making fatigue a somatisation disorder overlooks the fact that fatigue has both mental and physical components, thereby denying a possible organic aetiology to explain such fatigue".

"Furthermore, this emphasis on the lack of an organic basis favours missed diagnoses (e.g. fatigue and thyroid abnormalities, or fatigue and inflammation)".

"Inflammation is not a stable condition. In a given individual it can fluctuate rapidly according to a number of environmental factors (e.g. stressors) and internal variables (e.g. diurnal variation of cortisol)".

"Basic aspects of diagnosis of behavioural disorders remain controversial and lack solid scientific foundations".

"In order to provide consistency, all studies examining the potential impact of inflammatory pathways should include a standard set of inflammatory biomarkers (which should include) the acute phase proteins, CRP, sialic acid and haptoglobin; the inflammatory mediators, prostaglandins E2 and C3A and the innate immune cytokine IL-6 as measured by the high sensitivity (hs)-enzyme-linked immunosorbent assay (ELISA) in plasma. ***These biomarkers, especially hs-CRP and IL-6, have been found to reproducibly identify the presence of an activated immune response in a number of disorders****. Most of these assessments can be run in certified commercial or hospital laboratories".*

"Proinflammatory cytokines induce the production of several downstream inflammatory mediators, such as prostaglandins and nitric oxide. Proinflammatory cytokines and other inflammatory mediators are produced by accessory immune cells, such as macrophages and monocytes in the periphery, and microglia within the central nervous system".

"Peripheral infections can sensitise or exaggerate existing brain inflammatory processes (and) elevated cytokine levels in blood have the potential to reverberate and activate central nervous inflammatory systems".

The Conclusions of the Review note the intense discussion at the meeting that resulted in a series of recommendations for improving understanding of the relationship between inflammation and subjective health complaints.

These recommendations note that because inflammation-associated sickness symptoms are a major impediment to human health, research on the mechanisms and treatment of such symptom burden in physically ill patients should be strongly encouraged; that clinical tools for assessing inflammation-associated symptoms should be standardised; that there should be a minimum set of inflammatory biomarkers; that brain neuroimaging techniques should be used for revealing the brain structures that are influenced by peripheral inflammatory processes and whose ability to process information is impaired by excessive amounts of interoceptive stimuli (**caused, it seems, not – as asserted by Wessely School psychiatrists -- by aberrant focusing on normal bodily sensations or by "remembered illness" but by inflammatory processes),** and that the high presence of inflammation-associated symptoms in physically ill patients provides a background against which it is possible to test alleviating effects of therapies targeting immune-to-brain communication pathways.

Documented immune system abnormalities in ME/CFS

1986

"Eighty percent of patients demonstrate clinically significant IgE mediated allergic disease, including food and drug reactions. The data indicate that patients have a high association with hypersensitivity states. Percent positive responsiveness to allergens is consistent with the high degree of allergy observed in these patients" (George B Olsen, James F Jones et al. J All Clin Immunol 1986:78:308-314).

1987

Irving Salit, Associate Professor of Medicine and Microbiology at the University of Toronto and Head of the Division of Infectious Diseases at Toronto General Hospital, noted: "*Findings include mild immunodeficiency, slightly low complement, anti-DNA antibodies and elevated synthetase, which is an interferon-associated enzyme commonly increased in infections.* ***This illness is of major importance because it is so prevalent and because it has such devastating consequences: afflicted patients are frequently unable to work or carry on with usual social activities.*** *We have found that a wide variety of infections may precipitate this illness (including Coxsackie B and mycoplasma). Some patients have mild elevations of IgM or IgG (and) low levels of anti-nuclear antibody. Patients tend to tolerate medications very poorly and many have a history of drug allergies. Most patients do not improve on anti-depressants and are usually exquisitely sensitive to the side effects. It is important for the physician to understand their suffering. There are enough abnormalities of organic disease to suggest that (it) is not purely a psychological ailment"* (Clin Ecol 1987/8:V:3:103-107).

1987

US clinicians and researchers who became world leaders in ME/CFS (including Paul Cheney, Daniel Peterson and Anthony Komaroff) noted: "*These studies demonstrated that a majority of patients with (ME)CFS have low numbers of NKH1^{+}T3^{-} lymphocytes, a population that represents the great majority of NK cells in normal individuals. (ME)CFS patients had normal numbers of NKH1^{+}T3^{+} lymphocytes, a population that represents a relatively small fraction of NK cells in normal individuals. When tested for cytotoxicity against a variety of different target cells, patients with (ME)CFS consistently demonstrated low levels of killing. In humans, studies suggest a correlation between low NK activity and serious viral infections in immunocompromised hosts.* ***We have carried out extensive phenotypic and functional characterisation of NK cells in patients with this syndrome (and have) found that the majority had abnormally low numbers of NKH1^{+} cells.*** *Further characterisation of such cellular subset abnormalities and the resulting alteration in quantitative and qualitative NK cytotoxic function will hopefully improve our understanding of the immunopathogenesis of this illness"* (M Caliguri et al. The Journal of Immunology 1987:139:10: 3306-3313).

1988

"Allergies are a common feature of patients with the chronic fatigue syndrome. Among the features of this syndrome is a high prevalence of allergy, an allergy that appears to be substantial" (Stephen E Straus et al: National Institutes for Allergy and Infectious Diseases. J Allergy Clin Immunol 1988:81:791-795).

1988

"*We report patients (who) had a specific deficiency of IgG1 subclass. The finding of IgG1 subclass deficiency in these patients is novel, as lone deficiency of this subclass is rare and affected patients appear to have common variable hypogammaglobulinaemia. Further scrutiny of cases (of ME/CFS) may reveal a range of subtle immunological abnormalities"* (Robert Read, Gavin Spickett et al. Lancet, January 30 1988:241-242).

1989

"Our investigations suggest that (ME)CFS is characterized by objective laboratory abnormalities. A more appropriate name for this syndrome would be chronic fatigue-immune dysfunction syndrome (CFIDS), since immune dysfunction appears to be the hallmark of the disease process" (Nancy Eby et al. In: Natural Killer Cells and Host Defense. Ed: Ades EW and Lopez C. 5th International Natural Killer Cell Workshop. Pub: Karger, Basel, 1989:141-145).

1989

"Many of the immunological and physical features of ME/CFS cannot be explained by mental illness" (Stephen E Straus of the National Institutes for Allergy and Infectious Diseases, USA, "USA Today", 13th April, 1989: reported in CFIDS Chronicle, Spring 1989, pp77-78).

1989

"(ME)CFS has been associated with abnormal T cell function. These patients have diminished phytohaemagglutinin-induced lymphocyte transformation and decreased synthesis of interleukin. We studied the display of CD3, CD5, CD2, CD4, CD8 and Leu-M3-defined antigen in peripheral blood mononuclear cells in (ME)CFS who fulfilled the (1988 Holmes et al) criteria. Patients had reduced expression of CD3. These data indicate that in (ME)CFS, some patients have T lymphocytes (CD2- and CD5- positive cells) without immunoreactive CD3" (ML Subira et al. The Journal of Infectious Disease 1989:160:1:165-166).

1989

"Disordered immunity may be central to the pathogenesis of (ME)CFS. Reduced IgG levels were common (56% of patients), with the levels of serum IgG3 and IgG1 subclasses particularly affected. The finding of significantly increased numbers of peripheral blood mononuclear cells that express Class-II histocompatibility antigens (HLA-DR) in our patients implies immunological activation of these cells. Once activated, these cells may continue to produce cytokines which may mediate the symptoms of (ME)CFS" (AR Lloyd et al. The Medical Journal of Australia 1989:151:122-124).

1990

"The subgroup of patients with immunological abnormalities may have a prolonged illness" (DO Ho-Yen JRCGP 1990:40:37-39).

1990

"In order to characterise in a comprehensive manner the status of laboratory markers associated with cellular immune function in patients with this syndrome, patients with clinically defined (ME)CFS were studied. ***All the subjects were found to have multiple abnormalities in these markers. The pattern of immune marker abnormalities observed was compatible with a chronic viral reactivation syndrome. A substantial difference in the distribution of lymphocyte subsets of patients with (ME)CFS was found when compared with normal controls.*** *Lymphocyte proliferation after PHA and PWM stimulation was significantly decreased in patients (by 47% and 67% respectively) compared with normal controls. Depression of cell-mediated immunity was noted in our study population, with over 80% of patients having values below the normal mean. The present report confirms that a qualitative defect is present in these patients' NK cells (which) might represent cellular exhaustion as a consequence of persistent viral stimulus. Results from the present study indicate that there is an elevation in activated T cells.* ***A strikingly similar elevation in $CD2^+$ $CDw26^+$ cells has been reported in patients with multiple sclerosis.*** *In summary, the results of the present study suggest that (ME)CFS is a form of acquired immunodeficiency. This deficiency of cellular immune function was present in all the subjects we studied"* (Nancy G Klimas et al. Journal of Clinical Microbiology 1990:28:6:1403-1410).

1990

"*(A) subnormal number of CD8 lymphocytes, a raised serum IgE level and a positive VP1 antigen are sufficiently frequent to suggest that they should become part of the routine screening of such patients.* ***In the present ME study, patients show a 40% incidence of both clinical and laboratory evidence of atopy.*** *It has been shown that T cell deficiency, particularly of the suppressor subset, can predispose to atopy without a genetic family history.* ***We have undertaken extensive T cell subset measurements in normal subjects subjected to psychological stress and would point out in none of these did we see CD8 levels as low as in some 40% of our ME patients"*** (JR Hobbs, JA Mowbray et al. Protides of Biological Fluids 1990:36:391-398).

1991

"*Compared with controls, (ME)CFS patients showed an increase in CD38 and HLA-DR expression.* ***These data point to a high probability (90%) of having active (ME)CFS if an individual has two or more of the CD8 cell subset alterations. Laboratory findings among (ME)CFS patients have shown low level autoantibodies, which may reflect an underlying autoimmune disorder****. A persistent hyperimmune response of the remaining CD8 cells might lead to an outpouring of cellular products and cytokines (eg. interferon, tumour necrosis factor, interleukin-1) that are characteristically associated with myalgia, fatigue, (and) neurological signs and symptoms associated with acute viral infections.* ***Unless the immune system is brought back into balance, this chronic activation affects the individual further and might eventually lead to other clinical illnesses"*** (Alan L Landay et al. Lancet 1991:338:707-712).

1991

"*Various abnormalities revealed by laboratory studies have been reported in adults with (ME)CFS. Those most consistently reported include depressed natural killer cell function and reduced numbers of natural killer cells; low levels of circulating immune complexes; low levels of several autoantibodies, particularly antinuclear and antithyroid antibodies; altered levels of immunoglobulins (and) abnormalities in number and function of lymphocytes"* (Buchwald and Komaroff et al; Reviews of Infectious Diseases 1991:13 (Suppl 1): S12- S28).

1991

"The NK (natural killer) cell is a very critical cell in (ME)CFS because it is clearly negatively impacted. ***The most compelling finding was that the NK cell cytotoxicity in (ME)CFS was as low as we have ever seen it in any disease. This is very, very significant data****. In (ME)CFS the actual function was very, very low --- 9% cytotoxicity: the mean for the controls was 25. In early HIV and even well into ARC (AIDS related complex, which*

often precedes the fully developed condition), NK cytotoxicity might be around 13 or 14 percent. ***(ME)CFS patients represent the lowest cytotoxicity of all populations we've studied"*** (Nancy Klimas, Professor of Medicine, University of Miami School of Medicine; Director of Immunology; Director of AIDS Research and Director of the Allergy Clinic at Miami. Presentation: Immunological Markers in (ME)CFS. The CFIDS Association Research Conference, November 1990, Charlotte, North Carolina. Reported in CFIDS Chronicle, Spring 1991; pp 47-50).

1991

"Despite the broad divergence of opinion in the medical community, there is little doubt that classic allergy and atopy are inexplicably prevalent in (ME)CFS. In a recent study, a high proportion (50%) of patients were found to be reactive to a variety of inhalant or food allergens when inoculated epicutaneously in the classic manner. Certainly patients with (ME)CFS differ immunologically from their healthy counterparts and it is this observation, more than any other today, that is evoked in support of the organic hypothesis of disease causation" (Stephen E Straus. Review of Infectious Diseases 1991:13: Suppl 1: S2-S7).

1992

A major study looking at neurological, immunological and virological aspects in 259 (ME)CFS patients found that neurological symptoms, MRI findings and lymphocyte phenotyping studies suggest that patients ***"may have been experiencing a chronic, immunologically mediated inflammatory process of the central nervous system"*** and that *" We think that this is probably a heterogeneous illness that can be triggered by different environmental factors (including stress, toxins and infectious agents), all of which can lead to immune dysfunction and the consequent reactivation of latent viruses"* (D Buchwald, Paul Cheney, Daniel Peterson, Robert C Gallo, Anthony Komaroff et al. Ann Int Med 1992:116:2:103-113).

1993

At the 1993 Los Angeles Conference on (ME)CFS, evidence was presented by Professor Nancy Klimas from the University of Miami that she and her team have been able to accurately predict 88% of (ME)CFS patients with a mathematical model of immunological parameters. This model combines levels of activated T cells and CD4 inducers of cytotoxic T cells with NK cell count and function: "*In a normal population, 20% of lymphocytes are active at any given time. 'In (ME)CFS, up to 80% of the cells are working'.* ***These lymphocytes and cytokines are so up-regulated that they cannot be driven any harder. It is as if they have been pushed as far as they can go and the immune system is completely exhausted"*** (CFIDS Chronicle: Summer 1993).

1993

"Using the immunophenotypic data presented, we were able to demonstrate that almost 50% of (ME)CFS patients, especially those with severe symptoms, showed signs of $CD8^+$ cell activation and an abnormal suppressor / cytotoxic $CD8^+$ cell ratio. ***Our observations strongly suggest that a large population of (ME)CFS patients have immunologic disorders and that their symptoms could be explained by a chronic immune activation state (and) that (ME)CFS represents a type of autoimmune disease in which a chronically activated immune system reacts against the host****. The 3:1 female/male ratio would not be unexpected: autoimmune syndromes are more common in women.* ***Because of the autoreactive nature of this condition, it might also lead to other immune disorders, such as well-recognised autoimmune diseases and multiple sclerosis"*** (Jay A Levy et al. Contemp Issues Infec Dis 1993:10:127-146).

According to Dr Elizabeth Dowsett, former President of the ME Association, at least 13% of ME/CFS patients are indistinguishable from patients with multiple sclerosis (personal communication).

1994

"The chronic fatigue immune dysfunction syndrome (CFIDS) is a major subgroup of the chronic fatigue syndrome (CFS). We and other investigators have reported a strong association between immune dysfunction and a serological viral activation pattern among patients in this group. This finding appeared similar to that for a variety of conditions, such as chronic active hepatitis and systemic lupus erythematosus*, in which a definite association between a particular HLA-DR/DQ haplotype and increased disease frequency has been reported.* ***We thus elected to examine a cohort of patients with CFIDS, with use of HLA-DR/DQ typing****.* ***A significant association between CFIDS and the presence of HLA-DQ3 was noted****. The association with HLA-DQ3 could represent an additive effect for patients who also have HLA-DR4 and/or HLA-DR5. (Our) results are intriguing. DQ3 was significantly more prevalent in patients than controls. It is possible that DR4 and DR5 are also associated with an increased risk of developing CFIDS.* ***These findings strongly suggest that further evaluation of persons with CFIDS, including an investigation of an HLA Class I linkage dysequilibrium, are warranted****. The data presented herein suggest that CFIDS, together with a variety of immune-mediated diseases, may share similar sequences of pathogenic mechanisms (and) in a subpopulation (of CFIDS), a genetic predisposition may be triggered immunologically by any number of potential stimuli,* ***resulting in a state of chronic immune dysequilibrium****. This model could easily explain findings with regard to viral infection (and) allergies"* (RH Keller, N Klimas et al. Clin Inf Dis 1994:18: (Suppl 1): S154-156).

1994

"These data suggest a correlation between low levels of NK cell activity and severity of CFIDS. Compromised or absent natural immunity is associated with acute and chronic viral infections such as AIDS, CFIDS and various immunodeficiency syndromes*. Stratification of patients with CFIDS into distinct groups according to the severity or duration of physical abnormalities might allow identification of laboratory abnormalities that are associated with severity.* ***The fact that NK cell activity decreases with increased severity and duration of certain clinical variables suggests that measurement of NK cell function could be useful for stratification of patients and possibly for monitoring therapy for and / or the progression of CFIDS****"* (EA Ojo-Amaize et al. Clin Inf Dis 1994:18: (Suppl 1):S157-159).

1994

"The immune system is a readily accessible, sensitive indicator of environmental or internal changes, and studies conducted by different groups over the past few years have provided valuable evidence for changes in immune status among individuals with (ME)CFS. To gain insight into the nosology and aetiology of (ME)CFS, we assessed patterns of soluble immune mediator expression at the protein and mRNA levels in individuals with (ME)CFS. ***The data presented in this report are consistent with previous evidence of immune dysregulation among patients with (ME)CFS and point to a dysregulation of TNF*** *(tumour necrosis factor)* ***expression as a distinctive feature of this condition****. Imbalances in TNF and associated changes in levels of other cytokines may underlie many of the characteristic features of (ME)CFS.* ***In addition, TNF-α can have deleterious effects on the central nervous system****"* (Roberto Patarca, Nancy G Klimas et al. Clin Inf Dis 1994:18: (Suppl 1):S147-153).

Tumour necrosis factor is a cytokine involved in systemic inflammation. Its primary role is in the regulation of immune cells. Increased TNF causes apoptosis, inflammation and tumorigenesis.

1994

"The up-regulated 2-5A pathway in (ME)CFS is consistent with an activated immune state and a role for persistent viral infection in the pathogenesis of (ME)CFS. The object of this study was to measure key parameters of the 2-5A synthetase/RNase-L antiviral pathway in order to evaluate possible viral involvement in (ME)CFS. The data presented suggest that 2-5A synthetase/RNase L pathway is an important biochemical indicator of the anti-viral state in (ME)CFS. ***Evidence that this pathway is activated in (ME)CFS was identified in this subset of severely disabled individuals as related to virological and immunologic status. This pathway phenotype could***

result from chronic over-stimulation due to chronic viral reactivation" (RJ Suhadolnik et al. Clin Inf Dis 1994:18(Suppl 1):S96-S104).

1994

"In the study of a complex illness such as (ME)CFS, the most important aspect is case definition*. Patients whose symptoms are primarily related to upper respiratory tract infections may have different precipitating agents and pathogenesis than those with predominantly gastrointestinal disturbances. It has been noted for a number of years that a history of allergies appears to be an important risk factor for (ME)CFS.* ***In addition to a history of allergy, other factors, such as exposure to chemicals, were noted to be possible triggers****.* ***The spectrum of illnesses associated with a dysregulated immune system now must include (ME)CFS***" (Paul H Levine. Clin Inf Dis 1994:18(Suppl 1):S57-S60).

1994

"Abnormalities of immune function, hypothalamic and pituitary function, neurotransmitter regulation and cerebral perfusion have been found in patients with (ME/CFS). Recent research has yielded remarkable data. The symptoms of (ME)CFS have long been viewed as a neurologic pattern, as confirmed by other names such as myalgic encephalomyelitis. A link is being forged between the symptoms pattern of (ME)CFS and objective evidence of central nervous system dysfunction. The view that (ME)CFS is a primary emotional illness has been undermined by recent research" (David S Bell: Instructor in Paediatrics, Harvard Medical School: Chronic fatigue syndrome update: Findings now point to CNS involvement: Postgraduate Medicine 1994:98:6:73-81).

1995

"One rationale for the immunological approach stems from the experience accumulated with similar syndromes such as autoimmune and environmentally-triggered diseases. (ME)CFS may be associated with certain HLA Class II antigens, as are some forms of environmental disease. These observations underscore the distinction between (ME)CFS and psychiatric maladies. Viruses are frequently reactivated in association with immune system dysregulation in (ME)CFS and may contribute to symptomatology" (Roberto Patarca. JCFS 1995:vol I:3/4:195-202).

1996

An important paper from Konstantinov and Tan et al demonstrated the occurrence of autoantibodies to a conserved intracellular protein (lamin B1), **which provides laboratory evidence for an autoimmune component in ME/CFS**. The authors found that 52% of patients with ME/CFS develop autoantibodies to components of the nuclear envelope (NE), mainly nuclear lamins, suggesting that in addition to the other documented disturbances of the immune system, **humoral autoimmunity against polypeptides of the NE is a prominent immune derangement in ME/CFS.** 67% of ME/CFS patients were positive for NE reactivity compared with 10% of normal controls. **Autoantibodies to NE proteins are relatively infrequent and most fall into the category of an unusual connective tissue disease characterised by brain or skin vasculitis.** The authors concluded that such activation ***"could be the result of various triggering agents, such as infections or environmental toxins. Future work should be directed at a better understanding of the autoimmune response of (ME)CFS patients to other NE antigens***" (K Konstantinov et al. J Clin Invest 1996:98:8:1888-1896).

1996

In 1996, Hilgers and Frank developed a score for severity of ME/CFS to correlate with parameters of immune activation. This was effected by a 30-point criteria score, basic laboratory programmes and immunological profiles in 505 patients. In addition, tests of the complement system, immune activation markers, hormones and viral / bacterial intracellular serology were evaluated. Seventeen significant

symptoms not currently in the CDC case definition were added, these being respiratory infections, palpitations, dizziness, dyspepsia, dryness of mouth / eyes, allergies, nausea, paraesthesia, loss of hair, skin alterations, dyscoordination *(sic)*, chest pain, personality changes, eczema, general infections, twitches and urogenital infections. A significant correlation between the criteria score and immunological parameters could be evaluated in 472 of the 505 patients. **The data confirm that a reduced or unstable immune control or delayed immune reaction to persisting viruses or bacterial intracellular pathogens, possibly triggered by common infections or other environmental factors, can lead to a chronic neuroimmune activation state and autoimmune disorders** (JCFS 1996:2: (4):35-47).

1997

"The level of bioactive transforming growth factor β was measured in serum from patients with (ME)CFS and compared with normal controls, patients with major depression, patients with systemic lupus erythematosus and patients with multiple sclerosis. ***Patients with (ME)CFS had significantly higher levels of bioactive TGFβ than the healthy controls, patients with major depression, patients with systemic lupus erythematosus and patients with multiple sclerosis****. Of greatest relevance to (ME)CFS are the effects of TGF β on cells of the immune and central nervous systems. There is accumulating evidence that TGFβ may play a role in autoimmune and inflammatory diseases"* (AL Bennet, AL Komaroff et al. J Clin Virol 1997:17:2:160-166).

1997

"(ME)CFS is associated with dysregulation of both humoral and cellular immunity, including mitogen response, reactivation of viruses, abnormal cytokine production, diminished natural killer (NK) cell function, and changes in intermediary metabolites*. The biochemical and immunologic data presented here identified a subgroup of individuals with (ME)CFS with an RNase L enzyme dysfunction that is more profound than previously observed (and) is consistent with the possibility that the absence of the 80-kDa and 40-kDa RNase L and presence of the LMW RNase L correlate with the severity of (ME)CFS clinical presentation"* (Robert Suhadolnik, Daniel Peterson, Paul Cheney et al. Journal of Interferon and Cytokine Research 1997:17:377-385).

Professor Suhadolnik explained in lay terms the significance of this paper (reported by Patti Schmidt in CFIDS Chronicle, Summer 1997, page 17): "*He has found a particular place in the immune system, the 2-5 RNase L antiviral pathway, where something is wrong. 'The whole antiviral pathway heats up out of control' explained Suhadolnik.* ***'You're really sick physiologically. Your body just keeps going and going like the Energiser bunny, making ATP and breaking it down. No wonder you're tired'****. He's found a novel protein in CFIDS patients in that viral pathway. 'In most cases, the human body is able to resist infection thanks to a cascade of biochemical events triggered by the body's immune system. If these antiviral defence pathways are functioning correctly, the spread of the virus is prevented'. Suhadolnik believes that (ME)CFS patients' bodies are responding to a central nervous system virus that interferes with their viral pathways' ability to fight off infection ".*

1997

A highly-respected paper by Vojdani and Lapp et al stressed the importance of cell apoptosis (and the pivotal role of protein kinase RNA in this) in ME/CFS: ***"A prominent feature of (ME)CFS is a disordered immune system.*** *Recent evidence indicates that induction of apoptosis might be mediated in a dysregulated immune system by the up-regulation of growth inhibitory cytokines. The purpose of this study was to evaluate the apoptotic cell population, interferon-α and the IFN-induced protein kinase RNA (PKR) gene transcripts in the peripheral blood lymphocytes of (ME)CFS individuals, as compared to healthy controls.* ***One of the distinguishing manifestations of (ME)CFS is abnormal immune function, characterised by a decreased NK cell-mediated cytotoxic activity, reduced mitogenic response to lymphocytes, altered cytokine production, elevated titres of antibodies to a number of viruses, and abnormal production of interferon (IFN).*** *The induction of apoptosis through immune defence mechanisms is an important mechanism for elimination of cancer cells as well as virus-infected cells. In the present study, the up-regulation of IFN-α and the IFN-induced PRK in (ME)CFS individuals is accompanied by the induction of apoptosis. In addition, dysregulation of cell cycle progression is associated with the*

induction of apoptosis in (ME)CFS individuals. ***Quantitative analysis of apoptotic cell population in (ME)CFS individuals has shown a statistically significant increase compared to healthy controls. The population of apoptotic cells in 76% of (ME)CFS individuals was well above the apoptotic cell population in the control cells.*** *Activation of PKR can result in induction of apoptosis. This activation of the PRK pathway could result from (a) dysregulated immune system or chronic viral infection"* (A Vojdani et al. Journal of Internal Medicine 1997:242:465-478).

1997

"*Previous studies from this laboratory have demonstrated a statistically significant dysregulation in several key components of the 2' 5'A synthetase / RNase L and PKR antiviral pathways in (ME)CFS. The 2-5A synthetase I RNase L pathway is part of the antiviral defence mechanism in mammalian cells. An accumulating body of evidence suggests that (ME)CFS is associated with dysregulation of both humoral and cellular immunity, including mitogen response, reactivation of viruses, abnormal cytokine production, diminished natural killer (NK) cell function and changes in intermediary metabolites. Marked and striking differences have been observed in the molecular mass and RNase L enzyme activity of 2-5A binding proteins in extracts of PBMC from individuals with (ME)CFS compared with healthy controls.* ***The biochemical and immunological data presented in this paper have identified a potential subgroup of individuals with (ME)CFS with an RNase L enzyme dysfunction that is more profound than previously observed in (ME)CFS,*** *and which the authors believe is related to the severity of (ME)CFS symptoms"* (Daniel L. Peterson, Paul R. Cheney, Kenny de Meirleir et al; Journal of Interferon and Cytokine Research 1997:17:377-385).

1998

"The increased expression of Class II antigens and the reduced expression of the co-stimulatory receptor CD28 lend further support to the concept of immunoactivation of T-lymphocytes in (ME)CFS and may be consistent with a viral aetiopathogenesis in the illness. ***We report, for the first time, increased expression of the apoptosis repressor protein bcl-2 (and) we demonstrated changes in different immunological parameters, each of which correlated with particular aspects of disease symptomatology (and) measures of disease severity****"* (IS Hassan, WRC Weir et al. Clin Immunol & Immunopathol 1998:87:1:60-67).

1998

*"The purpose of this study was to investigate the relationship between immunologic status and physical symptoms in (ME)CFS patients. The findings suggest that the degree of cellular immune activation is associated with the severity of (ME)CFS physical symptoms. Specifically, elevations in the T-helper / inducer cells, activated T-cells, activated cytotoxic / suppressor T-cells, and CD4 / CD8 ratio are associated with greater disease severity***"** (Immunological Status Correlates with Severity of Physical Symptoms in Chronic Fatigue Syndrome Patients. S Wagner N Klimas et al Presented at the Fourth International AACFS Research & Clinical Conference on CFIDS 1998: Mass. USA. Abstract page 28).

1999

*"****It is of great importance to develop biomarker(s) for differentiation between viral induced (ME)CFS (without sensitivity to chemicals) versus chemically-induced (ME)CFS.*** *Since interferon induced proteins 2-5A Synthetase and Protein Kinase RNA (PKR) have been implicated in the viral induction of (ME)CFS, the objective of this study was to utilise 205A and PKR activity for differentiation between (ME)CFS induced by either viruses or chemicals. A clear induction of 2-5A and PKR was observed when MDBK cells were exposed to HHV6, MTBE, and benzene.* ***We conclude that 2-5A and PKR are not only biomarkers for viral induction, but biomarkers to other stressors that include (chemicals)****"* (Vojdani A, Lapp CW. Immunopharmacol Immunotoxicol 1999:21(2):175-202).

1999

An article from researchers at the Institute of Immunology in Moscow discussed immunity impairment as a result of neurohormonal disorders and noted that at the base of (ME)CFS lie disturbances of the central nervous system, the endocrine system and the immune system: ***"It was found back in 1987/8 that there is an increase in the level of HLA DR and IL-2 receptors and an increase in the ratio CD4/CD8 in patients suffering from this syndrome"*** (Artsimovich NG et al. Russ J Immunol 1999:4(4):343-345).

2000

"The purpose of the present study was to investigate the relationship between immunologic status and physical symptoms in (ME)CFS. ***(Results) revealed significant associations between a number of immunologic measures and severity of illness. Specifically, elevations of T-helper/inducer cells, activated T cells, activated cytotoxic/suppressor T cells, and CD4/CD8 ratio were associated with greater severity of several symptoms. Furthermore, reductions in T-suppressor/cytotoxic cells also appeared related to greater severity of some (ME)CFS-related physical symptoms and illness burden****"* (SE Cruess, Nancy Klimas et al. JCFS 2000:7(1):39-52).

2000

"Blood and lymph nodes samples were obtained from patients with (ME)CFS. While a greater proportion of T lymphocytes from both lymph nodes and peripheral blood of (ME)CFS patients are immunologically naïve, the proportions of lymphocytes with a memory phenotype predominate in lymph nodes and peripheral blood of (ME)CFS patients. ***(ME)CFS has been proposed to be a disease of autoimmune aetiology and in this respect it is interesting to note that decreased proportions of CD45RA+T (naïve) cells are also seen in the peripheral blood of patients with autoimmune diseases****"* (Mary Ann Fletcher, Nancy Klimas et al. JCFS 2000:7(3):65-75).

2000

A major and detailed Review of the immunology of (ME)CFS was published by internationally-renowned immunologists Professors Robert Patarca and Nancy Klimas, together with the distinguished long-time ME/CFS research immunologist Mary Ann Fletcher. It contains 212 references. It is clear that people with (ME)CFS have two basic problems with immune function: (1) immune activation and (2) poor cellular function. These findings have a waxing and waning temporal pattern consistent with episodic immune dysfunction. The interplay of these factors can account for the perpetuation of (ME)CFS with remission / exacerbation cycles. The Review considers the evidence of immune cell phenotypic distributions; immune cell function; cytokines and other soluble immune mediators; immunoglobulins; autoantibodies; circulating immune complexes; Type I to Type II cytokine shift and the relationship between stressors, cytokines and symptoms. The data summarised indicate that (ME)CFS is associated with immune abnormalities that can account for the physiopathological symptomatology, and **recommends that future research should further elucidate the cellular basis for immune dysfunction in (ME)CFS and its implications** (JCFS 2000:6(3/4):69-107).

2001

"*Of significant interest was the fact that, of all the cytokines evaluated, the only one to be in the final model was IL-4 (which) suggests a shift to a Type II cytokine pattern. Such a shift has been hypothesised, but until now convincing evidence was lacking"* (Hanson et al; Clin Diagn Lab Immunol 2001:8(3)658-662).

2001

"There is considerable evidence already that the immune system is in a state of chronic activation in many patients with (ME)CFS" (Anthony Komaroff, Assistant Professor of Medicine, Harvard Medical School: American Medical Association Statement, Co-Cure, 17 July 2001).

2002

"The present review examines the cytokine response to acute exercise stress. The magnitude of this response bears a relationship to the intensity of effort but many environmental factors also modulate cytokine release. ***The main source of exercised-induced IL-6 production appears to be the exercising muscle. Cytokine concentrations are increased in (ME)CFS. Exercise-induced modulations in cytokine secretion may contribute to allergies (and) bronchospasm****"* (Shepherd RJ. Crit Rev Immunol 2002:22(3):165-182).

2003

A study was carried out by Belgian researchers to determine whether bronchial hyper-responsiveness (BHR) in patients with (ME)CFS is caused by immune system abnormalities. Measurements included pulmonary function testing, histamine bronchoprovocation test, immunophenotyping and ribonuclease (RNase) latent determination. There were 137 (ME)CFS participants. *"****Seventy three of the 137 patients presented with bronchial hyper-responsiveness. The group of patients in whom BHR was present differed most significantly from the control group, with eight differences in the immunophenotype profile in the cell count analysis, and seven differences in the percentage distribution profile. We observed a significant increase in cytotoxic T-cell count and in the percentage of BHR+ patients. Immunophenotyping of our sample confirmed earlier reports on chronic immune activation in patients with (ME)CFS compared to healthy controls, (with) BHR+ patients having more evidence of immune activation****"* (Nijs J, De Meirleir K, McGregor N et al. Chest 2003:123(4):998-1007).

2003

Japanese researchers focused on immunological abnormalities against neurotransmitter receptors in (ME)CFS using a sensitive radioligand assay. They examined serum autoantibodies to recombinant human muscarinic cholinergic receptor 1 (CHRM1) and other receptors in patients with (ME)CFS and the results were compared with those in patients with autoimmune disease and with healthy controls. The mean anti-CHRM1 antibody index was significantly higher in patients with (ME)CFS and with autoimmune disease than in controls. **Anti-nuclear antibodies were found in 56.7% of patients with (ME)CFS. The patients with positive autoantibodies to CHRM1 had a significantly higher score of 'feeling muscle weakness' than negative patients among (ME)CFS patients. The authors conclude: "***Autoantibodies to CHRM1 were detected in a large number of (ME)CFS patients and were related to (ME)CFS symptoms****. Our findings suggest that subgroups of (ME)CFS are associated with autoimmune abnormalities of CHRM1"* (Tanaka S, Kuratsune H et al. Int J Mol Med 2003:12(2):225-230).

2003

Looking at complement activation in (ME)CFS in the light of the need to identify biological markers in (ME)CFS, US researchers used an exercise challenge to induce symptoms of (ME)CFS and to identify a marker that correlated with those symptoms. *"****Exercise challenge induced significant increases of the complement split product C4a at six hours after exercise only in the (ME)CFS group****"* (Sorensen B et al. J All Clin Immunol 2003:112(2):397-403).

2003

"(ME)CFS is an increasing medical phenomenon leading to high levels of chronic morbidity*. The aim of this study was to screen for changes in gene expression in the lymphocytes of (ME)CFS patients. In a small but well-characterised population of (ME)CFS patients, differential display has been used to clone and sequence genetic markers that are over-expressed in the mononuclear cells of (ME)CFS patients.* ***Many researchers have recognised that current methods of diagnosis lead to the selection of a heterogeneous sample, and these data support that view.*** *It is encouraging that the wide 'spread' of data seen in (ME)CFS patients is not seen in the control samples.* ***The data presented here add weight to the idea that (ME)CFS is a disease characterised by over-expression of genes, some of which are known to be associated with immune system activation.*** *Identifying the triggering events for the induction of these genes will increase our understanding of this disease.* ***Some interesting possibilities include viral infection, neuroendocrine disturbances, and allergen exposure. A link with allergy may be particularly pertinent since approximately 80% of (ME)CFS patients are atopic. Some of the genes identified in this study may therefore be linked with the increase in allergic effects seen in (ME)CFS****"* (R Powell, S Holgate et al. Clin Exp Allergy 2003:33:1450-1456).

2003

In an Invited Review, Patrick Englebienne from the Department of Nuclear Medicine, Vrije University, Brussels, explained in simple terms the significance of RNase L: *"RNase L (2-5-oligoadenylate-dependent ribonuclease L) is central to the innate cellular defence mechanism induced by Type I interferons during intracellular infection. In the absence of infection, the protein remains dormant. Recent evidence indicates, however, that the protein is activated in the absence of infection and may play a role in cell differentiation (and) immune activation.* ***A de-regulation of this pathway has been documented in immune cells of (ME)CFS patients. This protein escapes the normal regulation (resulting in) a cascade of unwanted cellular events.*** *Recent data indicate that the RNase L system role is not limited to the cell defence mechanism against intracellular infection but extends to the complete innate and adaptive immune systems, including NK and T-cell proliferation and activation, as well as to cell differentiation and proliferation.* ***The presence of unregulated active RNase L fragments in immune cells may lead to deleterious effects which are inherent to the cellular targets of the protein (because) an unregulated destruction of rRNA and of mitochondrial RNA leads to cell apoptosis. Should the RNase L de-regulation exist in muscle cells, it would necessarily restrain normal muscular development and hence activity (and) muscular weakness is a common feature of (ME)CFS****"* (JCFS 2003:11(2):97-109).

2004

"The exacerbation of symptoms after exercise differentiates (ME)CFS from several other fatigue-associated disorders. Research data point to an abnormal response to exercise in patients with (ME)CFS compared to healthy sedentary controls, and to an increasing amount of evidence pointing to severe intracellular immune dysregulation in (ME)CFS patients. The dysregulation of the 2-5A synthetase/RNase L pathway may be related to a channelopathy, capable of initiating both intracellular hypomagnesaemia in skeletal muscles and transient hypoglycaemia. This might explain muscle weakness and the reduction of maximal oxygen uptake, as typically seen in (ME)CFS patients. The activation of the protein kinase R enzyme, a characteristic feature in at least a subset of (ME)CFS patients, might account for the observed excessive nitric oxide (NO) production in patients with (ME)CFS. Elevated NO is known to induce vasodilation, which may cause and enhance post-exercise hypotension" (J Nijs, K De Meirleir, N McGregor, P Englebienne et al. Med Hypotheses 2004:62(5):759-765).

2004

"Immunological aberration (in ME/CFS) may be associated with an expanding group of neuropeptides and inappropriate immunological memory. Vasoactive neuropeptides act as hormones, neurotransmitters, immune modulators and neurotrophes. They are immunogenic and known to be associated with a range of autoimmune conditions. They are widely distributed in the body, particularly in the central, autonomic

and peripheral nervous systems and have been identified in the gut, adrenal gland, reproductive organs, vasculature, blood cells and other tissues. They have a vital role in maintaining vascular flow in organs and are potent immune regulators with primary anti-inflammatory activity. They have a significant role in protection of the nervous system (from) toxic assault. *This paper provides a biologically plausible mechanism for the development of (ME)CFS based on loss of immunological tolerance to the vasoactive neuropeptides following infection or significant physical exercise. Such an occurrence would have predictably serious consequences resulting from the compromised function of the key roles these substances perform"* (Staines DR. Med Hypotheses 2004:62(5):646-652).

2004

"Patients (with ME/CFS) are more likely to have objective abnormalities of the immune system than control subjects. We measured the frequency of certain HLA antigens (and) restricted our analysis to Class II molecules, as these appear to be more specific predictors of susceptibility to immunologically-based disorders. ***The frequency of the HLA-DQ1 antigen was increased in patients compared to controls. This association between (ME)CFS and the HLA-DQ1 antigen translates into a relative risk of 3.2"*** (RS Schacterle, Anthony L Komaroff et al. JCFS 2004:11(4):33-42).

2004

"(ME)CFS is a serious health concern (and) studies have suggested an involvement of the immune system. ***A Symposium was organised in October 2001 to explore the association between immune dysfunction and (ME)CFS, with special emphasis on the interactions between immune dysfunction and abnormalities noted in the neuroendocrine and autonomic nervous systems of individuals with (ME)CFS.*** *This paper represents the consensus of the panel of experts who participated in this meeting (which was co-sponsored by the US Centres for Disease Control and the National Institutes of Health).* ***Data suggest that persons with (ME)CFS manifest changes in immune responses that fall outside normative ranges. It has become clear that (ME)CFS cannot be understood based on single measurements of immune, endocrine, cardiovascular or autonomic nervous system dysfunction. The panel encourages a new emphasis on multidisciplinary research into (ME)CFS.*** *The panel recommends the implementation of longitudinal studies that include the following key elements: well-characterised cases and controls; assays designed to measure immune function: (a) natural killer cell activity; (b) percentage of peripheral blood lymphocytes expressing activation markers; (c) pro-inflammatory cytokines and soluble receptors; (d) Th-1 and Th-2 responses; (e) activity of the 2-5A synthetase pathway, and (f) serum immunoglobulin levels; selected measures of autonomic nervous system and neuroendocrine functioning; functional magnetic resonance imaging studies; studies to demonstrate the presence or absence of viral/microbial genetic material****. The use of interdisciplinary, multi-site (including international) longitudinal studies to explore links between the variations noted in (ME)CFS patients' immune, neuroendocrine, and cardiovascular systems is critical. Three primary methodological barriers impair the investigations of (ME)CFS: poor study design, the heterogeneity of the CFS population, and the lack of standardised laboratory procedures. The quality of previous CFS research (is hampered by) multiple differences in methods of subject recruitment and classification (and) clinical definitions applied and outcome measures used. It is our obligation to overcome the methodological barriers outlined above"* (Gerrity TR et al. Neuroimmunomodulation 2004:11(6):351-357).

2004

"Many patients with (ME)CFS have symptoms that are consistent with an underlying viral or toxic illness. *Because increased neutrophil apoptosis occurs in patients with infection, this study examined whether this phenomenon also occurs in patients with (ME)CFS.* ***Patients with (ME)CFS had higher numbers of apoptotic neutrophils, lower numbers of viable neutrophils, and increased expression of the death receptor, tumour necrosis factor receptor-1 on their neutrophils than did healthy controls. These findings provide new evidence that patients with (ME)CFS have an underlying detectable abnormality in their immune cells"*** (Kennedy G et al. J Clin Pathol 2004:57(8):891-893).

Commenting on this paper, Dr Neil Abbot, Director of Operations at ME Research UK, noted: "*The new paper by Dr Gwen Kennedy (MERGE Research Fellow) and colleagues reports evidence of increased neutrophil apoptosis (programmed cell death) in ME/CFS patients. Neutrophils represent 50-60% of the total circulating white blood cells and are fundamental to the functioning of an intact immune system.* ***The data presented in this report are consistent with the presence of an underlying, detectable abnormality in immune cell behaviour of many ME/CFS patients, consistent with an activated inflammatory process, or a toxic state***" (Co-Cure RES MED 30th July 2004).

2005

"Arguments exist as to the cause of (ME)CFS. Some think that it is an example of symptom amplification indicative of psychogenic illness, while our group thinks that some (ME)CFS patients may have brain dysfunction. We did spinal taps (lumbar puncture) on (ME)CFS patients. ***We found that significantly more (ME)CFS patients had elevations either in protein levels or numbers of cells than healthy controls and (some) patients had protein levels and cell numbers that were higher than laboratory norms. In addition, of the 11 cytokines detectable in spinal fluid, (some) were lower in patients than in controls (and some) were higher in patients. The results support two hypotheses: that some (ME)CFS patients have a neurological abnormality and that immune dysregulation within the central nervous system may be involved in this process.*** *A recent study showing elevations of IL-8 and IL-10 levels during chemotherapy-induced symptoms resembling some of those seen in (ME)CFS provides additional evidence for this hypothesis"* (Benjamin H Natelson et al. Clin Diagn Lab Immunol 2005:12(1):52-55).

2005

An article in The Scientist pointed out the need to measure cytokines in diverse disorders: "*The immune system is often likened to the military. The body's army has weapons such as antibodies and complement, and soldiers such as macrophages and natural killer cells. The immune system sports an impressive communications infrastructure in the form of intracellular protein messengers called cytokines and the cellular receptors that recognise them. The cytokine family consists of such soluble growth factors as the interleukins, interferons, and tumour necrosis factor, among others.* ***Their measurement has become an integral part of both clinical diagnostics and biomedical research***" (JP Roberts. The Scientist 2005:19:3:30).

It needs to be noted that the NICE Clinical Guideline 53 proscribes such measurements in people with ME/CFS, as did the MRC's "CFS/ME Research Advisory Group Research Strategy" Report of 1st May 2003, as did the CMO's Report of 2002, and as did the Joint Royal Colleges Report (CR54) of 1996.

2005

"Hyperactivation of an unwanted cellular cascade by the immune-related protein RNase L has been linked to reduced exercise capacity in persons with (ME)CFS. This investigation compares exercise capabilities of (ME)CFS patients with deregulation of the RNase L pathway and CFS patients with normal regulation. The results implicate abnormal immune activity in the pathology of exercise intolerance in (ME)CFS and are consistent with a channelopathy involving oxidative stress and nitric-oxide toxicity" (Snell CR et al. In Vivo 2005:19(2):387-390).

2005

*"****Diminished NK cell cytotoxicity is a frequently reported finding (in ME/CFS****). However, the molecular basis of this defect has not been described. Perforin is a protein found within intracellular granules of NK and cytotoxic T cells.* ***Quantitative fluorescence flow cytometry was used to the intracellular perforin content in (ME)CFS subjects and healthy controls. A significant reduction in the NK cell associated perforin levels in samples from (ME)CFS patients compared to healthy controls was observed. There was also an indication of a reduced perforin level within the cytotoxic T cells of (ME)CFS subjects, providing the first evidence (of) a T***

cell associated cytotoxic deficit in (ME)CFS. Because perforin is important in immune surveillance and homeostatis of the immune system, its deficiency may prove to be an important factor in the pathogenesis of (ME)CFS and its analysis may prove useful as a biomarker in the study of (ME)CFS" (Maher KJ, Klimas NG, Fletcher MA. Clin Exp Immunol 2005:142(3):505-511).

2005

"Previous research has shown that patients with (ME)CFS present with an abnormal exercise response and exacerbations of symptoms after physical activity. The highly heterogeneous nature of the CFS population and the lack of uniformity in both diagnostic criteria and exercise testing protocols preclude pooling of data. Still, we conclude that at least a subgroup of CFS patients present with an abnormal response to exercise. Importantly, the exacerbation of symptoms after exercise is seen only in the (ME)CFS population and not in fatigue-associated disorders such as depression*. Earlier (studies) revealed that in (ME)CFS patients, irrational fear of movement is not related to exercise performance.* ***The aim of this study was to examine the interactions between several intracellular immune variables and exercise performance in (ME)CFS. These data add to the body of literature showing impairment of intracellular immunity in patients with (ME)CFS. The results provide evidence for an association between intracellular immune dysregulation and exercise performance in patients with (ME)CFS"*** (J Nijs, N McGregor, K De Meirleir et al. Medicine & Science in Sports & Exercise 2005:Exercise Immunology in CFS:1647-1654).

2005

"The hypothesis of the present study is that the appearance of cell-specific autoimmune antibodies may define subsets of (ME)CFS. ***(ME)CFS is clinically similar to several autoimmune disorders that can be diagnosed and characterised by autoantibody profiles****. For this reason, we conducted an exhaustive evaluation of 11 ubiquitous nuclear and cellular autoantigens in addition to two neuronal specific antigens. Very few studies have evaluated the presence of autoantibodies in people with (ME)CFS. The findings of this study hint that evaluation of certain autoantibodies may give clues to on-going pathology in subsets of (ME)CFS subjects.* ***Among (ME)CFS subjects, those who had been sick longer had higher rates of autoantibodies****"* (S Vernon et al. Journal of Autoimmune Diseases May 25th, 2005:2:5).

2006

*"****The diagnostic criteria of CFS define a heterogeneous population composed of several subgroups. This study was designed to examine NK cell activity as a potential subgroup biomarker. The results (provide) evidence in support of using NK cell activity as an immunological subgroup marker in (ME)CFS. Improved treatment options will only come with better understanding of the syndrome's underlying pathophysiology. The present study specifically investigated the existence of an immunological subgroup of CFS patients.*** *Reduced NK cell activity may contribute to enhanced cytokine production.* ***Given the role that NK cells play in targeting virally infected cells, a clinically significant reduction in NK cell activity may lead to activation of latent viruses and new viral infections. (ME)CFS is a misunderstood condition. Research in the last two decades has produced little advancement in the understanding of the pathophysiology of (ME)CFS. Unfortunately, this lack of progress seems to have further contributed to the belief among some members of the medical community that (ME)CFS is not an actual organic condition****"* (Scott D Siegel, Mary Ann Fletcher, Nancy Klimas et al. J Psychosom Res 2006:60:6:559-566).

2006

"(ME)CFS is a poorly defined medical condition which involves inflammatory and immune activation. The Type I interferon antiviral pathway has been repeatedly shown to be activated in the most afflicted patients. An abnormal truncated form of ribonuclease L (37-kDa RNase L) is also found in (ME)CFS patients and this protein has been proposed as a biological marker for (ME)CFS (M Fremont, K De Meirleir et al. JCFS 2006:13(4):17-28).

2007

"For decades, (ME)CFS patients were – and still are – dismissed as lazybones or hypochondriacs. ***Many medical doctors and insurance companies still assert that (ME)CFS is a mental condition. The mainstream treatment for (ME)CFS is CBT, which means that patients with (ME)CFS are being treated as having a mental illness with 'treatments' that do not treat any underlying cause. Doctors who treat (ME)CFS patients as suffering from an organic disorder and scientists who examine the biological causes of (ME) are often considered quacks by their colleagues (and) insurance companies, which are sometimes even officially supported by governments in their attempts to eliminate the scientific view that (ME)CFS is an organic disorder. The official acceptance of the latter obviously would mean that the national health care systems are obliged to financially support those patients who are now considered hypochondriacs and, therefore, may easily be suspended from the national health care systems. There is, however, evidence that (ME)CFS is a severe immune disorder with inflammatory reactions and increased oxidative stress. Maes et al show that patients with (ME)CFS show very high levels of nuclear factor kappa beta in their immune cells. NFkβ is the major mechanism which regulates inflammation and oxidative stress. Thus, the increased production of NFkβ in the white blood cells of patients with (ME)CFS is the cause of the inflammation and oxidative stress (seen) in (ME)CFS"*** (Maes et al. Neuroendocrinology Letters, 2007. http://www.michaelmaes.com/).

2007

"Recent research has evaluated genetic signatures, described biologic subgroups, and suggested potential targeted treatments. ***Acute viral infection studies found that initial infection severity was the single best predictor of persistent fatigue****. Studies of immune dysfunction (have) extended observations of natural killer cytotoxic cell dysfunction of the cytotoxic T cell through quantitative evaluation of intracellular perforins and granzymes. Other research has focused on a subgroup of patients with reactivated viral infection.* ***Our expanded understanding of the genomics of (ME)CFS has reinforced the evidence that the illness is rooted in a biologic pathogenesis that involves cellular dysfunction and interactions between the physiologic stress response and inflammation. A large body of evidence links (ME)CFS to a persistent viral infection. (ME)CFS patients exhibited a distinct immune profile compared with fatigued and non-fatigued individuals. These patients displayed increased anti-inflammatory cytokines. Investigators noted the tropism with brain and muscle and suggested that the neuroinflammation seen in neuroimaging studies of a subgroup of CFS patients may result from enteroviral infection. The clinical implications are consistent with an immune system that may allow viral reactivation and raises a concern for tumour surveillance as well. The preponderance of available research confirms that immune dysregulation is a primary characteristic of (ME)CFS. These advances should result in targeted therapies that impact immune function, hypothalamic-pituitary-adrenal axis regulation, and persistent viral reactivation"*** (Nancy G Klimas et al. Current Rheumatology Reports 2007:9:6:482-487).

2009

In "Contemporary Challenges in Autoimmunity", the Annals of the New York Academy of Sciences published several articles looking at autoimmunity in (ME)CFS. One such paper by Ortego-Hernandez et al states: "*In association with (ME)CFS physiopathology, immune imbalance, abnormal cytokine profile or cytokine genes, and decreased serum concentrations of complement components have been reported…Many studies have shown the presence of several autoantibodies in (ME)CFS patients. Antibodies to diverse cell nuclear components, phospholipids, neuronal components, neurotransmitters, as well as antibodies against some neurotransmitter receptors of the central nervous system have been described".* The authors consider the different types of antibodies that have been reported in (ME)CFS patients and consider in particular antibodies to nuclear components (52% of (ME)CFS patients are reported as having autoantibodies to components of the nuclear envelope, particularly to lamin B1 molecule); to neurotransmitters and receptors (especially to neurotransmitters such as serotonin (5H-T), adrenals, ACTH and to receptors such as muscarinic cholinergic receptor I and μ-opioid receptor 1), and to diverse microorganisms, noting that serum levels of IgA were significantly correlated to the severity of illness. The authors state that the results showed that enterobacteria might be involved in the

aetiology of (ME)CFS and that **an increased gut-intestinal permeability could cause dysregulation of the immune response to the LPS of gram-negative enterobacteria**. The authors note that for many years, enterovirus infection has been associated with (ME)CFS and they note: "***However, several negative studies, combined with the rise of the psychiatric 'biopsychosocial model' of (ME)CFS have led to a diminished interest in this area***" (Ann N Y Acad Sci 2009:1173:600-6009).

(For the avoidance of doubt, in the above paper the authors cite only two "negative studies" associated with enteroviral infection in (ME)CFS: the first by Lindh G et al [Scand J Infect Dis 1996:28:305-307] used the 1994 CDC criteria which do not exclude those with psychiatric disorder, and the second by McArdle A et al [Clin Sci 1996 90:295-300] was co-authored by Richard Edwards, known for his belief that *"many of the symptoms of these patients could be a consequence of their reduced habitual activities"* [Ergonomics 1988:31:11:1519-1527] and his objection to the publishing by the ME Association of *"substantial amounts of information on the 'disease' "*).

Documented hair loss in ME/CFS

1989

Hair loss is listed as a feature of ME/CFS, known as CFIDS in some quarters in the US (Chronic Fatigue and Immune Dysfunction Syndrome: A Patient Guide. CFIDS Association, North Carolina Newsletter 1989).

1991

Hair loss is listed in 20% of ME/CFS patients (The Disease of a Thousand Names. DS Bell. Pollard Publications, New York 1991).

1992

*"It is a rare woman with Chronic Fatigue Syndrome who has not had hair loss" (*Jay Goldstein. In: The Clinical and Scientific Basis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Ed: Byron M Hyde, Jay Goldstein, Paul Levine. The Nightingale Research Foundation, Ottawa, Canada 1992 pp 247-252).

1993

Hair loss is again listed as a symptom of ME/CFS *(*CFIDS Association of America Leaflet 1993*).*

1996

The authors developed a score for severity of (ME)CFS that correlated with parameters of immune activation and association with pathogens; they found that comparison of patients with healthy controls led to a 30-criteria score that included 17 further significant criteria in addition to the CDC (Fukuda 1994) criteria. Those further 17 criteria included loss of hair (Hilgers A, Frank J. Journal of Chronic Fatigue Syndrome 1996:2:4:35-47*).*

2001

"*His sleep pattern changed…and his hair and eye lashes began to fall" (*John Richardson. Journal of Chronic Fatigue Syndrome 2001:9: (3-4):15-19).

Documented abnormalities in the gastro-intestinal system

(see also Section 1 above: "Attempts to reclassify irritable bowel syndrome as a mental disorder").

1998

Hyman and Wasser found evidence that abdominal pain is due to unilateral segmental neuropathy and consider their findings to be of pathophysiological significance, since lymphocytes and other immune products are in intimate contact with the gut wall and would have an influence on both gut motility and luminal contents. The authors conclude that the classification of irritable bowel syndrome should be modified to include a subset of patients who have a combination of CFS and IBS (Gastrointestinal Manifestations of Chronic Fatigue Syndrome: JCFS 1998:4(1):43-52).

2000

Aaron et al noted a growing literature suggesting that IBS and CFS may commonly co-exist, and that lifetime rates of IBS were particularly striking in patients with CFS (92%) compared with controls (18%) (Arch Intern Med 2000:160(2):221-227).

2001

Skowera and Wessely et al demonstrated a high prevalence of serum markers of coeliac disease in patients with chronic fatigue syndrome and suggested: *"screening for coeliac disease should be added to the relatively short list of mandatory investigations in suspected cases of CFS"* (Journal of Clinical Pathology 2001:54:335-336).

2004

"Gastrointestinal symptoms are common in patients with (ME)CFS…GI symptoms in patients with (ME)CFS are associated with objective changes of upper GI motility….Abdominal pain is distressing, often requiring analgesia for relief. A previously unrecorded symptom in (ME)CFS patients is nocturnal diarrhoea, which disrupts an already disturbed sleep pattern. These observations indicate that there is measurable disturbance in upper gut motility corresponding with symptoms (and) the more prominent delay in liquid rather than solid emptying may point to a central rather than peripheral aetiology" (RB Burnett et al. BMC Gastroenterology 2004:4:32).

Because ME/CFS is a multi-system disorder, there are many references to gut dysfunction and symptomatology in ME/CFS patients documented throughout the ME/CFS literature.

Documented liver and spleen problems in ME/CFS

1959

"Hepatic enlargement was also noted…." (ED Acheson. Am J Med April 1959:569-595).

1977

"*Physical findings may include…hepatitis"* (AM Ramsay, EG Dowsett et al. BMJ 21st May 1977: 1350).

1987

"In many of these patients, the fatigue was associated with….splenomegaly or hepatomegaly…….palpable splenomegaly (was found in) 87% (and) palpable hepatomegaly (in) 20%…In addition to their severe and persistent

fatigue, case-patients were significantly more likely to have had palpable splenomegaly noted in their medical records" (Gary P Holmes et al. JAMA 1st May 1987:257:17:2297-2302).

1987

"*22% had mildly deranged liver function tests"* (BD Calder et al. JRCGP 1987:37:11-14).

1988

"There may be splenomegaly or hepatomegaly" (M. Fisher Portwood. Nurse Practitioner 1988:13:2:11-23).

1991

"Enlargement of the spleen and liver is also not unusual" (SA Daugherty, BE Henry, DL Peterson et al. Reviews of Infectious Diseases 1991:13 (Suppl 1):S39-44).

1993

Up to 20% of (ME)CFS patients were noted to have hepatomegaly and splenomegaly (Anthony L Komaroff. CFS: CIBA Foundation Symposium 173: John Wiley, Chichester, 1993:43-61).

1993

"A significant number of patients with ME have exactly the same liver abnormality…that is seen in Gilbert's syndrome" (Charles Shepherd, Perspectives, Medical Matters: September 1993: iv).

1997

"*CFIDS patients have been reported to have multiple (physical) findings (including) hepatomegaly"* (CM Jorge, PJ Goodnick. Psychiatric Annals 1997:27:5:365-366).

2000

*"Hepatitis was found in 13.6%" (*Fred Friedberg et al. J psychsom Res 2000:48:59-68).

2001

"Animals subjected to both chemicals and stress exhibited dramatic increase in blood brain barrier permeability. Histological changes were also present in the liver and were particularly severe when the combination was used" (MB Abou-Donia. Presented at The Alison Hunter Memorial Foundation Third International Clinical and Scientific Conference on ME, 1st-2nd December 2001, Sydney, Australia*).*

Documented respiratory abnormalities in ME/CFS

1989

Payne and Sloan noted exertional dyspnoea in ME/CFS, with lung function studies showing a reduced forced expiratory flow (70% of the predicted value) and abnormalities of small airways and gas transport that might lead to reduced exercise tolerance shown in these patients (Ann Intern Med 1989:111:10:860).

1996

De Lorenzo et al noted that compared with controls, patients with ME/CFS showed a significant reduction in all lung function parameters tested (Australia and New Zealand Journal of Medicine 1996:26:4:563-564).

1998

De Becker et al reported on the prevalence of respiratory symptoms in a cohort of ME/CFS subjects; patients showed a significant decrease in VC (vital capacity), possibly due to a significant increase of RV (residual volume) and the authors commented: "*These observations can, at least partially, explain the respiratory symptoms in these patients".* The researchers recorded cough, medical history of allergy, chest tightness, and a remarkably high incidence of bronchial hyper-responsiveness, but the major complaint was pronounced exercise-induced dyspnoea (Fourth International AACFS Research & Clinical Conference on ME/CFS, Massachusetts, October 1998).

2002

Farquhar et al studied blood volume in relation to peak oxygen consumption and physical activity: *"….hypovolaemia, through its interaction with central haemodynamics, would contribute to the exercise intolerance associated with this disorder. We examined blood volume, peak aerobic power, habitual physical activity, fatigue level and their inter-relations to understand the physiological basis of this disorder. Patients displayed a trend for a 9% lower blood volume and had a 35% lower peak oxygen consumption. Peak ventilation was significantly lower in the patients.* ***In conclusion, individuals with CFS have a significantly lower peak oxygen consumption compared with controls, indicating that blood volume is a strong physiological correlate of peak oxygen consumption in patients with CFS"*** (Am J Physiol Heart Circ Physiol 2002:282(1):H66-H71).

2009

Ravindran, Petrie and Baraniuk observed that CFS subjects complain of shortness of breath; they therefore assessed dyspnoea associated with five activities of daily living. The sum was the Dyspnoea Score, which was compared between CFS patients and healthy controls. The MVV% (maximum voluntary ventilation, which is the total volume of air exhaled during 12 seconds of rapid deep breathing) was significantly higher for CFS patients than controls, indicating that CFS subjects might exert considerable respiratory effort. The CFS group also reported higher chest discomfort intensity after the first spirometry series and they also complained of greater difficulty tolerating the MVV manoeuvre. Borg scores (a measure of breathlessness in relation to heart rate – see Section 4 below) were higher for CFS patients than controls after both the first and second sets of spirometry (Journal of Allergy and Clinical Immunology February 2009: S260: Abstracts).

Documented abnormal gene expression in ME/CFS

There are more abnormal genes in ME/CFS than there are in cancer (personal communication from a research scientist).

There can no longer be any doubt from both US and UK research that in ME/CFS there are proven abnormalities in numerous genes and that such abnormalities are acquired as a result of interactions with the environment as opposed to being hereditary.

Gene expression describes the behaviour of certain genes when attacked by an infection or other insult: some genes become over-active and produce chemicals that cause symptoms seen in ME/CFS, while other genes become under-active or shut down (The Chronic Fatigue Syndrome Research Foundation Newsletter 10, November 2004).

In the UK, Jonathan Kerr from London has been leading the CFS Research Foundation's work in this area: using micro arrays and Taqman PCR techniques, his team has found numerous genes to be abnormal and these genes showed problems in various body systems including the immune system, in neurological function and in mitochondrial metabolism (ie. in the production of cellular energy). As the CFSRF Newsletter of November 2004 made plain: *"It is clear that in ME/CFS patients the gene function has changed and these changes can be detected and measured"*.

In the US Suzanne Vernon and her team showed that differentially expressed genes are related to energy metabolism, muscle and immune response (T-cell associated chemokines and receptors) and that several of these genes are involved in transcriptional regulation, metabolism and the immune response; Vernon et al have put forward mechanisms possibly associated with exacerbation of symptoms in ME/CFS and with differences in how patients cope with stress compared with controls (Co-Cure 14th March 2005).

The key question associated with genetic abnormalities is whether or not the detected abnormalities are associated with changes in the *function* of the gene that would lead to changes in the gene product(s), so it is the *functional* changes that are critical to understanding the relevance of these observations. It is necessary to understand how the biochemical changes relate to the gene changes because it is the genetic changes that drive the biochemical processes associated with the gene product(s) --- in other words, the observed biochemical abnormalities are a reflection of gene abnormalities.

The work of US immunologist Roberto Patarca-Montero illustrates how changes in just one single gene can have wide-ranging consequences: he has identified an abnormal gene in ME/CFS patients that is multi-factorial, affecting the immune response to infection *and* the regulation of calcium and phosphate in bone metabolism *and* the expression of autoimmune disease, showing that acquired changes in a single gene can result in a compromised response to infection, to disordered calcium and phosphate metabolism and to increased susceptibility to autoimmune disease (Chronic Fatigue Syndrome, Genes, and Infection: the Eta-1 /Op Paradigm. Roberto Patarca-Montero, Howarth Medical Press, 2003).

Patarca-Montero's gene studies also reveal consequences within the cardiovascular system in respect of the response to injury of the normal artery wall: endothelial cell migration is stimulated through a co-operative mechanism with other gene products, and these gene products affect vascular permeability, compromising the cardiovascular system and the nerves and tissues it supplies, with potential implications for the ability to exercise without biological consequences that are damaging.

On 18th March 2008 The Daily Telegraph carried an item entitled "ME: 'Invisible disease' is now easier to read" by Bob Ward, who reported on Kerr's work (published in the Journal of Clinical Pathology and presented at an ME Research UK [MERUK] biomedical conference at the University of Cambridge on 6th May 2008). **The article pointed out that Kerr's team has identified 88 genes that produce different levels of proteins and other molecules in ME/CFS compared with controls.** In 2005 Kerr had carried out a complex analysis and found that patients with ME/CFS can be divided into seven clinical sub-types according to specific gene combinations and the severity of symptoms. **The most severely affected patients had 71 of the 88 gene abnormalities**. In his follow-up paper to which the Telegraph article referred, Kerr's earlier work was confirmed: (J Clin Pathol 2007: doi:10.1136/jcp.2007.053553) – see below.

There is now a substantial evidence-base demonstrating abnormal gene expression in ME/CFS patients and the following examples are barely illustrative:

2002

"The objective of this study was to determine if gene expression profiles of peripheral blood mononuclear cells (PBMC) could distinguish between subjects with CFS and healthy controls…..The classification algorithms grouped the majority of CFS cases together, and distinguished them from healthy controls…These results successfully demonstrate the utility of the blood for gene expression profiling to distinguish subjects with CFS from healthy controls (and) for

*identifying biomarkers…It is noteworthy that one gene, the CMRF35 antigen precursor, was detected as differentially expressed by all analytical approaches. This gene encodes a cell membrane antigen that is a member of the immunoglobulin superfamily (and) is thought to control interactions between T cells and antigen presenting cells or target (virus-infected or mutated) cells that have to be killed…**The CMRF35 antigen was highly expressed in the CFS group…All of these genes implicate immune dysfunction in the pathophysiology of CFS**"* (Suzanne D Vernon et al. Disease Markers 2002:193-199).

2004

*"We used differential-display PCR of PMBCs to search for candidate biomarkers for CFS….86% of the differences were present at baseline. Differential expression of ten genes was verified by real-time reverse transcription PCR: five (including perforin) were downregulated and the remaining five genes were upregulated…Many of these genes have known functions in defence and immunity, thus supporting prior suggestions of immune dysregulation in the pathogenesis of CFS…Differential-display PCR is a powerful tool for identification of candidate biomarkers…Six of the ten genes with verified differential expression have functions related to immune response**. **This adds strength to the theory that dysregulation of immunity plays a major role in the biology of CFS**"* (Martin Steinau et al. Journal of Molecular Medicine 2004: 10.1007/s00109-004-0586-4).

2005

To test the hypothesis that there are reproducible abnormalities of gene expression in (ME)CFS patients compared with healthy controls, Jonathan Kerr's team analysed and compared gene expression in peripheral blood mononuclear cells of ME/CFS patients with matched blood-donor controls. Sixteen genes were significantly different and were confirmed as having an expression profile associated with ME/CFS. "*These genes may be important in the pathogenesis of (ME)CFS and can be grouped according to immune, neuronal, mitochondrial and other functions…These findings are consistent with previous work showing that patients with (ME)CFS have evidence of immune activation, such as increased numbers of activated T cells and cytotoxic cells, and raised circulating cytokine concentrations…**NTE*** (neuropathy target esterase) ***is a target for organophosphates and chemical warfare agents, both of which may precipitate (ME)CFS**…. EIF2B4 is a mitochondrial translation initiation factor and one of the EIFB2 family, within which mutations have been shown to be associated with **central nervous system hypomyelination and encephalopathy…. The involvement of genes from several disparate pathways suggests a complex pathogenesis involving T cell activation and abnormalities of neuronal and mitochondrial function, and suggests possible molecular bases for the recognised contributions of organophosphate exposure and virus infection*" (N Kaushik, ST Holgate, JR Kerr et al. J Clin Pathol 2005:58:826-832).

(Neuropathy target esterase (NTE) is inhibited by several OP pesticides, chemical warfare agents, lubricants, and plasticisers, leading to OP-induced delayed neuropathy in humans, with over 30,000 cases of human paralysis -- Gary Quistad et al. PNAS June 24, 2003:100:13:7983-7987).

2006

*"The single most influential gene was sestin 1 (SESN1), supporting recent evidence of oxidative stress involvement in (ME)CFS…**results suggest a common link between oxidative stress, immune system dysfunction and potassium imbalance in (ME)CFS leading to impaired sympatho-vagal balance strongly reflected in an abnormal HRV*** (heart rate variability) (Gordon Broderick, Nancy Klimas et al. Pharmacogenomics 2006:7(3):407-419).

2006

In a study of cytokine genomic polymorphisms in (ME)CFS, Italian researchers found *"a highly significant increase in TNF-857 and CT genotypes among patients with respect to controls and a significant decrease of IFN gamma low producers among patients with respect to controls…**We hypothesise that (ME)CFS patients can have***

a genetic predisposition to an immunomodulatory response of an inflammatory nature probably secondary to one or more environmental insults" (N Carlo-Stella et al. Clin Exp Rhuematol 2006:24(2):179-182).

2007

Kerr et al reported in detail the genomic and phenotypic differences in 7 genomically-defined subtypes of CFS: "*In this study, for each CFS/ME subtype, we determined those genes whose expression differed significantly from that of normal blood donors. Genomic analysis was then related to clinical data for each CFS/ME subtype.* ***Genomic analysis revealed some common (neurological, haematological, cancer) and some distinct (metabolic, endocrine, cardiovascular, immunological, inflammatory) disease associations among the subtypes.*** *Subtypes 1,2 and 7 were the most severe, and subtype 3 was the mildest…****It is particularly interesting that in these genomically derived subtypes, there were distinct clinical syndromes… as would be expected in a disease with a biological basis****…****It has long been recognised that subtypes of CFS/ME exist*** (but Professor Anthony Pinching, Chairman of the Investment Steering Group that devised the process and criteria for setting up the CFS Clinics and who oversaw the assessment of bids and who allocated funds -- and who is lead advisor on "CFS/ME" to the Department of Health -- is on record in the CMO's Working Group 2002 Report (Annex 4: section 3) as asserting that subgrouping "*may be considered a matter of semantics and personal philosophy"*)…***It is intriguing that within our 88 gene signature, there are several genes with links to various aetiological triggering factors. For example, virus infection (EIF4G1, EB12) and organophosphate exposure (NTE). EIF4G1 is an eukaryotic translation initiation factor which is bound and cleaved by a range of viruses, including enteroviruses which both trigger and persistently infect CFS patients****….We have previously documented upregulation of NTE in (ME)CFS. NTE is the primary site of action of organophosphate (OP) compounds….****Exposure to OP compounds may trigger CFS/ME and Gulf War illness****"* (Jonathan Kerr et al. J Clin Pathol 2007: doi:10.1136/jcp.2007.053553).

Commenting on this paper, Dr Neil Abbot, Director of Operations at the charity ME Research UK, said:

"*These genes can be subdivided into categories by diseases and disorders or by molecular and cellular functions. The research team says that three of the genes identified are directly linked with mitochondrial function, and a further ten have indirect links with mitochondrial metabolism…*

Important disorders and functions associated with some of the genes in the putative ME/CFS gene 'signature' (include):

"Diseases: Haematological (22 genes); Immunological (14 genes); Cancer (31 genes); Dermatological (3 genes); Endocrine system (9 genes)

"Molecular and cellular function: Cellular development (26 genes): Cell death (33 genes); gene expression (31 genes); Cellular growth and proliferation (31 genes); Cellular assembly and organisation (15 genes)

"Physiological system development and function: Haematological system (22 genes); Nervous, immune and lymphatic system (18 genes); Tissue morphology (18 genes); Survival (17 genes); Immunity (20 genes)" (Breakthrough, Spring 2008:3).

2008

"We have reported the differential expression of 88 human genes in patients with CFS; 85 of these genes were upregulated and 3 downregulated. ***Highly represented functions were haematological disease and function, immunological disease and function, cancer, cell death, immune response and infection…Research studies have identified various features relevant to the pathogenesis of CFS/ME such as viral infection, immune abnormalities and immune activation, exposure to toxins, chemicals and pesticides….****Various studies have*

analysed the gene expression in peripheral blood of patients with CFS/ME ***and in all of these, genes of immunity and defence are prominent….Progress is being made towards an understanding of the pathogenesis of this intriguing and devastating disease"*** (Jonathan Kerr. Current Rheumatology Reports 2008:10:482-491).

2008

"…expression of several complement genes remained at higher level in CFS subjects before and post-exercise, ***indicating a lack of acute phase transcriptional response by these genes which may lead to localised and uncontrollable inflammation mediated tissue damage****"* (Sorensen B et al. Mol Med 2008: Nov 16: Epub ahead of print).

2009

"We used global transcriptome analysis to identify genes that were differentially expressed in the vastus lateralis muscle of female and male CFS patients. ***We found that the expression of genes that play key roles in mitochondrial function and oxidative imbalance…were altered, as were 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. We argue that these major biological processes could be involved in and/or responsible for the muscle symptoms of CFS****"* (Pietrangelo T, Fulle S et al. Int J Immunpathol Pharmacol 2009:22(3)795-807).

2009

Referring to earlier work that demonstrated 88 abnormal genes, the authors state: "*We set out to determine whether these findings were reproducible in fresh subjects (and) whether the previously-reported dysregulation of these genes also occurred in drug-free patients with endogenous depression…****Results show that these findings are reproducible, and that gene expression in endogenous depression patients was markedly different to that in CFS/ME patients and was similar to that in normal controls in terms of these 88 human genes****…In the present study, we have confirmed this differential expression in 62 additional and previously untested CFS/ME patients…****We have addressed the question of the specificity of these 88 genes to CFS/ME by testing drug-free patients with endogenous depression. The fact that only 5 of these genes were abnormally expressed in endogenous depression patients as compared with normals supports the view that CFS/ME and endogenous depression are biologically distinct, and that the psychological features of CFS/ME are in fact secondary to the pathogenesis****"* (Lihan Zang, Jonathn Kerr et al. J Clin Pathol 2009: doi 10.1136/jcp2009.072561).

Documented ocular abnormalities in ME/CFS

1988

David J Browning found that the most common ocular symptoms in ME/CFS (CFIDS) are floaters, transient blurring of vision, transient double vision, extreme light sensitivity, burning and pain in the eyes (CFIDS Chronicle October 1988:6-7).

1992

Nystagmus at a rate 230 times normal, poor fixation stability, and ratchet vision were reported (Meeting-Place 1992: 38:38-40).

1992

Potaznick and Kozol evaluated 25 ocular symptoms in 190 ME/CFS patients and concluded that the ocular symptoms are genuine and that for all but one symptom (teary eyes), the patients' responses were found to be statistically significant. The authors concluded: "*Statistical analysis shows that the increased rate at which patients with (ME/CFS) CFIDS report ocular symptoms is not explained by chance alone…Many patients experience very troubling and disabling symptoms"* (Optometry and Vision Science 1992:69:10:811-814).

1994

Potaznick and Kozol reported ocular symptomatology in relation to the visual, functional, perceptual and pathological aspects of the visual system and repeated their message that the symptoms are genuine (Clin Inf Dis 1994:18 (Suppl 1):S87).

1994

Caffery et al showed that ME/CFS affects the ocular system in many ways. The authors stated: "*It appears that the ocular system may be very much affected by this systemic disease. The objective findings of the anterior segment suggests an organic aetiology…The ocular neurological symptoms that presented in such a large number of ME/CFS patients suggests a possible neurological basis for this disease"* (Journal of the American Optometric Association 1994:65:187-191).

1997

Vedelago reported that the visual symptoms commonly encountered in ME/CFS patients include blurred vision, difficulty focusing, difficulty tracking lines of print, diplopia or ghosting of images, problems with peripheral vision, misjudging distances, inability to tolerate looking at moving objects, floaters and halos, intolerance to glare, grittiness, burning, dryness or itchiness and photophobia. Objective ocular findings included poor oculomotor control, exophoria (the tendency for one eye to diverge when the other eye is covered), remote near-point of convergence, poor convergence, constricted peripheral fields, incomplete blinking, small pupils, visual midline shift, and low grade chronic allergic conjunctivitis (The CFS Research Review 2000: 4-9).

Documented involvement of viruses in ME/CFS

1954

Describing an outbreak of infection of the central nervous system complicated by intense myalgia in late summer 1952 affecting nurses at the Middlesex Hospital, London, the author (ED Acheson, who later became UK Chief Medical Officer) reported the clinical features to be severe muscular pain affecting the back, limbs, abdomen and chest, with evidence of mild involvement of the central nervous system, diarrhoea, vomiting, respiratory distress, paresis and brain stem involvement that included nystagmus, double vision and difficulty in swallowing; additionally, bladder symptoms occurred in more than half the patients. Acheson highlighted this small outbreak because of the similarity to atypical poliomyelitis (ED Acheson. Lancet: Nov 20th 1954:1044-1048). The label of "atypical poliomyelitis" was originally given to ME (The Disease of a Thousand Names. David S Bell. Pollard Publications, Lyndonville, New York, 1991). **Many patients today experience exactly the symptoms described by Acheson, but such symptoms are dismissed by the Wessely School as somatisation and as hypervigilance to normal bodily sensations.**

1955

Acheson described and compared the outbreak at the Royal Free in 1955 with the outbreak at The Middlesex in 1952, noting the relatively prolonged active course of the disease, marked muscular pain and spasm, involvement of the lymph nodes, liver and spleen, tenderness under the costal margins, and ulcers in the mouth, all of which – if looked for and if not dismissed as somatising -- are still to be found in "pure" ME today (ED Acheson. Lancet: Aug 20th 1955:394-395).

1959

In his detailed review of numerous outbreaks of Benign Myalgic Encephalomyelitis from 1934, Acheson described the common characteristics of the disease and clinical picture, which included agonising muscular pain, headache, nausea, sensory disturbances, stiffness of the neck and back, dizziness, muscular twitching, tremor and in-coordination, localised muscular weakness, emotional lability, problems with memory and concentration, hyperacusis, somnolence and insomnia, with relapses being almost inevitable, together with variability of symptoms. Signs included hepatic enlargement, lymphadenopathy and evidence of CNS involvement, nystagmus being "*almost invariable"* in some of the outbreaks. The question of hysteria was addressed and discounted: "*Final points against mass hysteria as a major factor in the syndrome are the consistency of the course of the illness and the similarities in the symptoms…The disorder is not a manifestation of mass hysteria"* and Acheson specifically warned that the diagnosis of ME should be reserved for those with (virally induced) evidence of CNS damage: ***"If not, the syndrome will become a convenient dumping ground for non-specific illnesses characterised by fluctuating aches and pains, fatigue and depression****"*, exactly the situation that exists in the UK 50 years after Acheson's prophecy (ED Acheson. American Journal of Medicine, April 1959:569-595).

1978

*"The clinical picture was variable both in the time pattern of its progression and the severity of the symptoms…It became clear early on in the outbreak that there was organic involvement of the central nervous system (and) there was objective evidence of involvement of the central nervous system…The most characteristic symptom was the prolonged painful muscle spasms…Bladder dysfunction occurred in more than 25% of all the patients…****Case to case contact between patients and their relatives also occurred****…McEvedy and Beard's conclusions* (of mass hysteria) *ignore the objective findings of the staff of the hospital of fever, lymphadenopathy, cranial nerve palsies and abnormal signs in the limbs…Objective evidence of brain stem and spinal cord involvement was observed"* (Nigel D Compston. Postgraduate Medical Journal 1978:54:722-724).

1983

*"Virological studies revealed that 76% of the patients with suspected myalgic encephalomyelitis had elevated Coxsackie B neutralising titres (and symptoms included) malaise, exhaustion on physical or mental effort, chest pain, palpitations, tachycardia, polyarthralgia, muscle pains, back pain, true vertigo, dizziness, tinnitus, nausea, diarrhoea, abdominal cramps, epigastric pain, headaches, paraesthesiae, dysuria)….The group described here are patients who have had this miserable illness. Most have lost many weeks of employment or the enjoyment of their family (and) marriages have been threatened…" (*BD Keighley, EJ Bell. JRCP 1983:33:339-341).

1985

"…from an immunological point of view, patients with chronic active EBV infection appear 'frozen' in a state typically found only briefly during convalescence from acute EBV infection" (G Tosato, S Straus et al. The Journal of Immunology 1985:134:5:3082-3088. Note that "CFS" was then thought to be caused by EBV).

1985

"*Epstein-Barr virus infection may have induced or augmented an immunoregulatory disorder that persisted in these patients" (*Stephen E Straus et al. Ann Intern Med. 1985:102:7-16).

1985

*"The clinical, pathological, electrophysiological, immunological and virological abnormalities in 50 patients with the postviral fatigue syndrome are recorded. These findings confirm the organic nature of the disease (and) suggest that it is associated with disordered regulation of the immune system and persistent viral infection" (*PO Behan, WMH Behan, EJ Bell. Journal of Infection 1985:10:211-222.

1987

*"Ninety percent of the patients tested had antibodies to Epstein-Barr virus and 45% tested had antibodies to cytomegalovirus…if this fatigue syndrome is triggered by an infectious agent, an abnormal immune response may be involved" (*TJ Marrie et al. Clinical Ecology 1987:V:1:5-10).

1987

*"Recently associations have been found between Coxsackie B infection and a more chronic multisystem illness. A similar illness…has been referred to as… myalgic encephalomyelitis…140 patients presenting with symptoms suggesting a postviral syndrome were entered into the study…Coxsackie B antibody levels were estimated in 100 control patients…All the Coxsackie B virus antibody tests were performed blind…Of the 140 ill patients, 46% were found to be Coxsackie B virus antibody positive…This study has confirmed our earlier finding that there is a group of symptoms with evidence of Coxsackie B infection. We have also shown that clinical improvement is slow and recovery does not correlate with a fall in Coxsackie B virus antibody titre" (*BD Calder et al. JRCGP 1987:37:11-14).

1987

*"The illness has an acute onset after a variety of infections and then enters a chronic phase characterised by fatigue and numerous other symptoms….Other findings include a sleep disorder, mild immunodeficiency, slightly low complement, anti-DNA antibodies and elevated synthetase which is an interferon-associated enzyme commonly increased in viral infections" (*Irving E Salit. Clinical Ecology 1987:V:3:103-107).

1988

"These results show that chronic infection with enteroviruses occurs in many PVFS (post-viral fatigue syndrome, a classified synonym for ME/CFS) *patients and that detection of enterovirus antigen in the serum is a sensitive and satisfactory method for investigating infection in these patients….Several studies have suggested that infection with enteroviruses is causally related to PVFS…The association of detectable IgM complexes and VP1 antigen in the serum of PVFS patients in our study was high…This suggests that enterovirus infection plays an important role in the aetiology of PVFS" (*GE Yousef, EJ Bell, JF Mowbray et al. Lancet January 23rd 1988:146-150).

1988

"*Myalgic encephalomyelitis was thought for some time to be produced by a less virulent strain of poliovirus…**chronic, persistent viruses may often be reactivated during this illness…once reactivated, do these viruses then go on to produce many of the symptoms of the disease? And what reactivates these endogenous viruses? Could it be environmental toxins? Could it be infection with other, exogenous lymphotropic viruses?***" (Anthony L Komaroff. Journal of Virological Methods. 1988:21:3-10).

(In the light of the discovery in 2009 of the XMRV retrovirus – see below -- this paper by Professor Komaroff 21 years in advance of that discovery showed remarkable prescience).

1988

"*Postviral fatigue syndrome / myalgic encephalomyelitis… has attracted increasing attention during the last five years…Its distinguishing characteristic is severe muscle fatiguability made worse by exercise…The chief organ affected is skeletal muscle, and the severe fatiguability, with or without myalgia, is the main symptom. The results of biochemical, electrophysiological and pathological studies support the view that muscle metabolism is disturbed, but there is no doubt that other systems, such as nervous, cardiovascular and immune are also affected…Recognition of the large number of patients affected…indicates that a review of this intriguing disorder is merited….**The true syndrome is always associated with an infection**…Viral infections in muscle can indeed be associated with a variety of enzyme abnormalities…(Electrophysiological results) are important in showing the organic nature of the illness and suggesting that muscle abnormalities persist after the acute infection…there is good evidence that Coxsackie B virus is present in the affected muscle in some cases" (*PO Behan, WMH Behan. CRC Crit Rev Neurobiol 1988:4:2:157-178).

1988

*"The main features (of ME) are: prolonged fatigue following muscular exercise or mental strain, an extended relapsing course; an association with neurological, cardiac, and other characteristic enteroviral complications. Coxsackie B neutralisation tests show high titres in 41% of cases compared with 4% of normal adults…These (chronic enteroviral syndromes) affect a young, economically important age group and merit a major investment in research" (*EG Dowsett. Journal of Hospital Infection 1988:11:103-115).

1989

"Ten patients with post-viral fatigue syndrome and abnormal serological, viral, immunological and histological studies were examined by single fibre electromyographic technique….The findings confirm the organic nature of the disease. A muscle membrane disorder…is the likely mechanism for the fatigue and the single-fibre EMG abnormalities. This muscle membrane defect may be due to the effects of a persistent viral infection…There seems to be evidence of a persistent viral infection and/or a viral-induced disorder of the immune system…The infected cells may not be killed but become unable to carry out differentiated or specialised function" (Goran A Jamal, Stig Hansen. Euro Neurol 1989:29:273-276).

1990

*"Skeletal samples were obtained by needle biopsy from patients diagnosed clinically as having CFS (and) most patients fulfilled the criteria of the Centres for Disease Control for the diagnosis of CFS (Holmes et al 1988)…**These data are the first demonstration of persistence of defective virus in clinical samples from patients with CFS**…We are currently investigating the effects of persistence of enteroviral RNA on cellular gene expression leading to muscle dysfunction" (*L Cunningham, RJM Lane, LC Archard et al. Journal of General Virology 1990:71:6:1399-1402).

1990

*"Myalgic encephalomyelitis is a common disability but frequently misinterpreted…**This illness is distinguished from a variety of other post-viral states by a unique clinical and epidemiological pattern characteristic of enteroviral infection**…33% had titres indicative and 17% suggestive of recent CBV infection…Subsequently…31% had evidence of recent active enteroviral infection…**There has been a failure to recognise the unique epidemiological pattern of ME**…Coxsackie viruses are characteristically myotropic and enteroviral genomic sequences have been detected in muscle biopsies from patients with ME. **Exercise related abnormalities of function have been demonstrated by nuclear magnetic resonance and single-fibre electromyography including a failure to coordinate oxidative metabolism with anaerobic glycolysis causing abnormal early intracellular**

acidosis, consistent with the early fatiguability and the slow recovery from exercise in ME. *Coxsackie viruses can initiate non-cytolytic persistent infection in human cells. Animal models demonstrate similar enteroviral persistence in neurological disease… and* ***the deleterious effect of forced exercise on persistently infected muscles. These studies elucidate the exercise-related morbidity and the chronic relapsing nature of ME****"* (EG Dowsett, AM Ramsay et al. Postgraduate Medical Journal 1990:66:526-530).

1991

A paper reporting the discovery of a retrovirus associated with (ME)CFS (Retroviral sequences related to human T-lymphotropic virus type II in patients with chronic fatigue immune dysfunction syndrome. Elaine DeFreitas, Paul R Cheney, David S Bell et al. Proc Natl Acad Sci USA 1991:88:2922-2926) is addressed in detail in the section "The role of Viruses in ME/CFS".

1991

*"Persistent enteroviral infection of muscle may occur in some patients with postviral fatigue syndrome and may have an aetiological role….The features of this disorder suggest that the fatigue is caused by involvement of both muscle and the central nervous system…We used the polymerase chain reaction to search for the presence of enteroviral RNA sequences in a well-characterised group of patients with the postviral fatigue syndrome…53% were positive for enteroviral RNA sequences in muscle…Statistical analysis shows that these results are highly significant…On the basis of this study…****there is persistent enteroviral infection in the muscle of some patients with the postviral fatigue syndrome and this interferes with cell metabolism and is causally related to the fatigue****"* (JW Gow et al. BMJ 1991:302:696-696).

1991

"The findings described here provide the first evidence that postviral fatigue syndrome may be due to a mitochondrial disorder ***precipitated by a virus infection****…Evidence of mitochondrial abnormalities was present in 80% of the cases with the commonest change (seen in 70%) being branching and fusion of cristae, producing 'compartmentalisation'. Mitochondrial pleomorphism, size variation and occasional focal vacuolation were detectable in 64%…Vacuolation of mitochondria was frequent…In some cases there was swelling of the whole mitochondrion with rupture of the outer membranes…prominent secondary lysosomes were common in some of the worst affected cases…The pleomorphism of the mitochondria in the patients' muscle biopsies was in clear contrast to the findings in 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"* (WMH Behan et al. Acta Neuropathologica 1991:83:61-65).

1991

Considerations in the Design of Studies of Chronic Fatigue Syndrome. Reviews of Infectious Diseases. Volume 13, Supplement 1: S1 – S140. University of Chicago Press. Contributing authors included Anthony L Komaroff, David S Bell, Daniel L Peterson, Sandra Daugherty and Sheila Bastien, whose work has been referred to in other parts of this Report.

1991

Postviral Fatigue Syndrome. British Medical Bulletin 1991:47:4: 793-907. Churchill Livingstone.

This major publication, published by Churchill Livingstone for The British Council, includes papers by the Wessely School considered by some to be misrepresentative of ME/CFS (for example: "History of postviral fatigue syndrome" by S Wessely; "Postviral fatigue syndrome and psychiatry" by AS David -- in which David, a co-author of the Oxford criteria, confirmed that "*British investigators have put forward an alternative, less strict, operational definition which is essentially chronic…fatigue in the absence of neurological signs, (with)*

psychiatric symptoms…as common associated features" (AS David; BMB 1991:47:4:966-988) and "Psychiatric management of PVFS" by M Sharpe) but also contains the following:

"Molecular viral studies have recently proved to be extremely useful. They have confirmed the likely important role of enteroviral infections, particularly with Coxsackie B virus" (Postviral fatigue syndrome: Current neurobiological perspective. PGE Kennedy. BMB 1991:47:4:809-814)

"Our focus will be on the ability of certain viruses to interfere subtly with the cell's ability to produce specific differentiated products as hormones, neurotransmitters, cytokines and immunoglobulins etc in the absence of their ability to lyse the cell they infect. By this means viruses can replicate in histologically normal appearing cells and tissues…Viruses by this means likely underlie a wide variety of clinical illnesses, currently of unknown aetiology, that affect the endocrine, immune, nervous and other …systems" (JC de la Torre, P Borrow, MBA Oldstone. BMB 1991:47:4:838-851).

"*We conclude that persistent enteroviral infection plays a role in the pathogenesis of PVFS…The strongest evidence implicates Coxsackie viruses…Patients with PVFS were 6.7 times more likely to have enteroviral persistence in their muscles"* (JW Gow and WMH Behan. BMB 1991:47:4:872-885).

"The postviral fatigue syndrome (PVFS), with profound muscle fatigue on exertion and slow recovery from exhaustion seems to be related specifically to enteroviral infection. The form seen with chronic reactivated EBV infection is superficially similar, but without the profound muscle fatigue on exercise" (JF Mowbray, GE Yousef. BMB 1991:47:4:886-894).

1992

"We will report at the First International Research Conference on Chronic Fatigue Syndrome to be held at Albany, New York, 2-4 October 1992, our new findings relating particularly to enteroviral infection…We have isolated RNA from patients and probed this with large enterovirus probes…detailed studies...showed that the material was true virus…Furthermore, this virus was shown to be replicating normally at the level of transcription. Sequence analysis of this isolated material showed that it had 80% homology with Coxsackie B viruses and 76% homology with poliomyelitis virus, demonstrating beyond any doubt that the material was enterovirus" (Press Release for the Albany Conference, Professor Peter O Behan, University of Glasgow, October 1992).

1993

"Samples from 25.9% of the PFS (postviral fatigue syndrome) *were positive for the presence of enteroviral RNA, compared with only 1.3% of the controls…We propose that in PFS patients, a mutation affecting control of viral RNA synthesis occurs during the initial phase of active virus infection and allows persistence of replication defective virus which no longer attracts a cellular immune response"* (NE Bowles, RJM Lane, L Cunningham and LC Archard. Journal of Medicine 1993:24:2&3:145-180).

1993

"These data support the view that while there may commonly be asymptomatic enterovirus infections of peripheral blood, it is the presence of persistent virus in muscle which is abnormal and this is associated with postviral fatigue syndrome*…Evidence derived from epidemiological, serological, immunological, virological, molecular hybridisation and animal experiments suggests that persistent enteroviral infection may be involved in… PFS"* (PO Behan et al. CFS: CIBA Foundation Symposium 173, 1993:146-159).

1994

"Individuals with CFS have characteristic clinical and laboratory findings including…evidence of viral reactivation*…The object of this study was to evaluate the status of key parameters of the 2-5A synthetase/RNase L antiviral pathway in individuals with CFS who participated in a placebo-controlled, double-blind, multi-centre trial…The present work confirms the finding of elevated bioactive 2-5A and RNase L activity in CFS…RNase L, a 2-5A-dependent enzyme, is the terminal effector of an enzymatic pathway that is stimulated by either virus infection or exposure to exogenous lymphokines. Almost two-thirds of the subjects…displayed baseline RNase L activity that was elevated above the control mean"* (Robert J Suhadolnik, Daniel L Peterson, Paul Cheney et al. In Vivo 1994:8:599-604).

A note on the significance of this paper

Viral infections of cells results in the production and secretion of cytokines, including the interferons. Interferons control the way that cells respond to a virus by means of a group of inter-related enzymes that comprise an anti-viral pathway. This pathway is known as the 2',-5'-oligoadenylate synthetase/RNase L pathway.

RNase L (ribonuclease latent) is the key enzyme in the antiviral pathway and is designed to degrade viral RNA. It has to be "turned on" by a small molecule, 2-5 A. Binding of 2-5A to RNase L changes the enzyme from its latent (inactive) state to its active state. When active, RNase L inhibits viral protein synthesis and thereby prevents viral replication.

Several critical parts of the anti-viral pathway are not functioning correctly in ME/CFS.

The level of RNase L enzyme activity has been demonstrated to be upregulated (ie. increased) by as much as 1,500 times above normal levels, and researchers at Temple University School of Medicine, Philadelphia, have shown that not only is the activity of the RNase L enzyme significantly higher in patients with (ME)CFS than in controls, but also that there is a significant increase in the level of 2-5A (the molecule that converts RNase L from its latent to its active state) and in the level of 2-5A synthetase (the enzyme that synthesises the 2-5A activator molecule).

The most striking finding in patients with (ME)CFS is, however, that they have a unique form of the RNase L enzyme. The size of the RNase L protein is normally 80 kDa (kiloDaltons), but in many people with (ME)CFS, this 80 kDa enzyme is either scarce or missing altogether. Instead, a unique low molecular weight (LMW) form of RNase L is observed (30 kDa). Besides its smaller size, the LMW RNase L seen in (ME)CFS patients has other biochemical differences from the 80 kDa RNase L. The LMW RNase L binds its activator more tightly and is more potent than the 80 kDa form of RNase L.

Studies have revealed several connections between the RNase L pathway and the clinical status of (ME)CFS patients, demonstrating that the increased activity of the RNase L pathway is an indication of a lower state of health and that all three measurements of the pathway are abnormal in (ME)CFS.

Studies carried out in various countries apart from the US (including Australia, Belgium, France and Germany) have all confirmed the presence of the LMW RNase L in (ME)CFS; moreover, two different methods using different probes to detect RNase L accurately identified (ME)CFS patients.

Importantly, the RNase L ratio also distinguished individuals with (ME)CFS from those with fibromyalgia or depression.

In addition, studies have shown that the presence of LMW RNase L is independent of the duration of (ME)CFS symptoms: the LMW RNase L was detected in individuals who had (ME)CFS symptoms for as long as 19 years.

The presence of the LMW RNase L identifies a group of people with (ME)CFS who have an abnormally elevated anti-viral response, and the anti-viral RNase L protein level and enzyme activity are potentially powerful diagnostic tools for (ME)CFS (with grateful acknowledgement to Nancy Reichenbach, associate scientist in the Department of Biochemistry at Temple University School of Medicine, and to the CFIDS Association of America: http://www.cfids.org/archives/2000rr/2000-rr1-article01.asp).

Although these important abnormalities were known about in 1994, and despite the evidence of the reliability and reproducibility of RNase L testing that was presented in 1999 at the Second World Congress on (ME)CFS in Brussels, in the UK there has been continued opposition to such testing, not only by the Wessely School (who consistently advise that only limited investigations should be carried out), but also by the ME Association.

For example, the Medical Director of the ME Association, Dr Charles Shepherd, apparently intended to inform readers of the ME Association's Newsletter (Perspectives) that his view of the international work on RNase L was that it *"may involve what I and many of my colleagues regard as over-investigation for highly speculative abnormalities in antiviral pathway activity"*, which seemed to echo Professor Anthony Pinching's view that *"over-investigation can (cause patients) to seek abnormal test results to validate their illness"* (Prescribers' Journal 2000: 40:2:99-106). The Spring 2001 Issue of the ME Association's Medical and Welfare Bulletin stated (on page 9) about RNase L testing: "*Having discussed the possible value of this type of blood test with members of the MEA's Scientific and Medical Advisory Panel, there is general agreement that insufficient evidence exists to recommend that this test should be carried out for either diagnostic or management purposes"* (members of the SMAP included Professor Peter Behan, Professor Leslie Findley, Dr John Gow, Professor Anthony Pinching and Dr Shepherd himself).

The ME Association did, however, co-fund with The Linbury Trust studies examining RNase L activity: blood from patients attending the Fatigue Service at St Bartholomew's Hospital and from Romford, Essex, was sent to Dr John Gow, who was working with Professors Peter and Wilhelmina Behan and Dr Abhijit Chaudhuri, all then at the University of Glasgow. Gow et al's work on a total of 22 patients with CFS was published in Clinical Infectious Diseases (2001:33:12:2080-2081), the conclusion being that *"patients with CFS showed no significant activation"* of either part of the RNase L pathway, and that *"assay of antiviral pathway activation is unlikely to form a rational basis for a diagnostic test for CFS".*

Professors Suhadolnik and De Meirleir robustly showed that Gow et al's study was fundamentally flawed. Pointing out that *"Over the years, our teams have repeatedly observed an activation at the enzymatic level of the antiviral pathway in subsets of CFS patients"*, they noted that Gow et al had (1) misunderstood the established knowledge of the IFN pathway, (2) did not confirm their observations of genetic expression at the transcriptional level (which would have clarified their results), (3) used the terms "genetic expression" and "activity" interchangeably, when they are not necessarily synonymous (particularly when the research involves enzymes). They also noted that confusion in the mind of Gow et al about these issues led them to misquote their articles: "*On the basis of their limited observations, Gow et al challenge our observations and further deny any rational basis to our proposal regarding the use of 37-kDa RNase L detection as a biological marker for CFS. In our study, which they clearly misquoted, we did not measure the enzymatic activity of the fragment and, hence, the 2-5A pathway activation as Gow and colleagues claimed. Instead, we limited our study to the quantitative detection of the 37-kDa truncated enzyme…We observed a significant increase in the 37-kDa RNase L level in patients with CFS compared with that observed in healthy control subjects, patients with fibromyalgia, and patients with depression….Consequently, this does not support the claim that the presence of the 37-kDa RNase L in CFS could only be imparted to non-specific increases in the antiviral pathway activation…Our data demonstrate that there is a more comprehensive downstream cellular role for the signal transduction by IFN than what Gow and colleagues pretend to present to the readers of Clinical Infectious Diseases"* (Clin Inf Dis 2002:34:1420-1421).

The ME Association and its medical advisors, however, remained convinced that Gow et al were correct: "*A very important conclusion from this study is that costly investigations such as the RNase L test, which assess the amount of antiviral activity in ME/CFS, are unlikely to provide the basis for a diagnostic test. Such tests are therefore*

of very questionable value in the assessment of people with ME/CFS" (MEA Medical and Welfare Bulletin, Spring 2002, Issue No 6, page 10).

At the AACFS International Research Conference in 2003 held in Washington, Wilhelmina Behan, as co-author of the Gow et al study, was publicly challenged by Professor Suhadolnik to defend it, but was unable to so.

Notwithstanding, on the basis of the Gow / Behan results, the ME Association's Medical Advisor remains of the view that *"the presence of …abnormalities in antiviral pathways has been assessed in research studies funded by the ME Association"* and that the results of these tests are not *"of proven value"* (ME/CFS/PVFS: An exploration of the key clinical issues. Dr Charles Shepherd and Dr Abhijit Chaudhuri, for The ME Association, 2007).

In contrast to such UK views about the significance of RNase L, in 2000 Professor Anthony Komaroff from Harvard had written about Professor De Meirleir's work on RNase L in an Editorial in the American Journal of Medicine: *"What is this research telling us? It is another piece of evidence that the immune system is affected in chronic fatigue syndrome and it reproduces and extends the work of another investigator (Professor Suhadolnik from the US), lending credibility to the result"* (Am J Med 2000:108:169-171).

Eight years after the Second World Congress on (ME)CFS in Brussels, advised by psychiatrists of the Wessely School, the NICE Guideline of 2007 makes no mention of the abnormalities in the RNase L antiviral pathway and recommends limited serology testing for certain viruses only, **which exclude testing for Coxsackie B virus** (testing for EBV, a particular interest of Professor Peter White is, however, permitted).

Given that a classified synonym for ME/CFS is "post-viral fatigue syndrome" (ICD-10 G93.3) and given that the NICE Guideline purports to apply to people with "CFS/ME", it is striking that the Guideline states on page 141: "***Serological testing should not be carried out unless the history is indicative of an infection***". It is notable that the PACE Trial Investigators did not include virological testing of participants in their trial that is based on their theory that patients with "CFS/ME" are deconditioned, so it needs to be ascertained what, exactly, do the Wessely School psychiatrists understand the term "post-viral" to mean if not a history indicative of an infection?

It is worth noting that elevated levels of RNase L are associated with reduced maximal oxygen consumption (VO_2 max) and exercise duration in ME/CFS patients; Snell et al found that both abnormal RNase L activity and low oxygen consumption were observed in most (ME)CFS patients, findings that demonstrate that patients' extremely low tolerance for physical activity is likely to be linked to abnormal oxidative metabolism, perhaps resulting from defective interferon responses (Comparison of maximal oxygen consumption and RNase L enzyme in patients with CFS. C Snell et al. AACFS Fifth International Research and Clinical Conference, Seattle, January 2001; #026).

It is also worth noting that the 37 kDa LMW RNase L fragment found in ME/CFS patients is produced by cleavage of calpain (an apoptotic enzyme), and the whole process affects the calcium and potassium ion channels, a channelopathy that will lead to low body potassium (a known finding in ME-CFS patients -- Burnett et al found that total body potassium (TBK) was lower in patients with (ME)CFS and suggest that abnormal potassium handling by muscle in the context of low overall body potassium may contribute to fatigue in (ME)CFS (Medical Journal of Australia, 1996:164:6:384).

It is also important to note that patients who express the low molecular weight RNase L may have problems with enzymatic detoxification pathways, particularly in the liver. This is significant because of the resultant adverse effect on thyroid function.

It has long been noted by practitioners that ME/CFS patients are often clinically hypothyroid even though biochemically euthyroid. Evidence suggests that such patients may not really be euthyroid, especially at the tissue level. (Chopra IJ. J Clin Endocrinol Metab 1997:82(2):329-334), so particular attention needs to be paid

to investigating the bioavailablity of T3 because in ME/CFS, T3 levels are often low (or at the low end of the normal range). Consequently, selenium levels need to be investigated in patients with ME/CFS who have reduced T3 levels: this is because selenium (as selenocysteine) is an integral component of two important enzymes, glutathione peroxidase and iodothryonine deiodinase; it is expressed in the liver and it regulates the conversion of thyroxine (T4) to the active and more potent T3. Individuals who have a deficiency of 5′ deiodinase cannot produce T3 from T4, thus it is necessary to establish baseline levels of selenium in ME/CFS patients whose T3 levels are low.

In the UK, the NICE Guideline does not recommend such testing.

In relation to RNase L, a recent literature review of the immunological similarities between cancer and (ME)CFS pointed out:

"Cancer and CFS are both characterised by fatigue and severe disability (and) certain aspects of immune dysfunctions appear to be present in both illnesses…A literature review of overlapping immune dysfunctions in CFS and cancer is provided. ***Abnormalities in ribonuclease (RNase L)*** *and hyperactivation of nuclear factor kappa-beta (NF-kappaβ) are present in CFS and in prostate cancer. Malfunctioning of natural killer (NK) cells has long been recognised as an important factor in the development and recurrence of cancer, and has been documented repeatedly in CFS patients.* ***The dysregulation of the RNase L pathway****, hyperactive NF-kappaβ leading to disturbed apoptotic mechanisms and oxidative stress or excessive nitric oxide, and low NK activity may play a role in the two diseases (and)… are present in both diseases. These anomalies may be part of the physiopathology of some of the common complaints, such as fatigue"* (Meeus M et al. Anticancer Res 2009:29(11):4717-4726).

It seems that, even if not a specific biomarker for ME/CFS, the significance of the abnormal RNase L anti-viral pathway in ME/CFS patients cannot be sufficiently emphasised, but through the undoubted influence of the Wessely School, ME/CFS sufferers in the UK are not permitted to have their anti-viral pathway status investigated.

1994

Chronic Fatigue Syndrome: Current Concepts. Clinical Infectious Diseases 1994: Volume 18: Supplement 1: S1 – S167. Ed. Paul H Levine. University of Chicago Press. Contributing authors include: Paul H Levine, Alexis Shelokov, Anthony L Komaroff, David S Bell, Paul R Cheney, Leonard H Calabrese, Leonard A Jason, Seymour Grufferman, Hirohiko Kuratsune, Charles Bombadier, Nancy G Klimas, Mary Ann Fletcher, Roberto Patarca-Montero, Benjamin H Natelson, Robert J Suhadolnik, Daniel L Peterson, Dharam V Ablashi, Fred Friedberg, Jay A Levy, Peter O Behan, Wilhelmina MH Behan and Mark O Loveless.

In his Summary of the Viral Studies of CFS, Dr Dharam V Ablashi concluded: ***"The presentations and discussions at this meeting strongly supported the hypothesis that CFS may be triggered by more than one viral agent…Komaroff suggests that, once reactivated, these viruses contribute directly to the morbidity of CFS by damaging certain tissues and indirectly by eliciting an on-going immune response"*** (Clin Inf Dis 1994:18 (Suppl 1):S130-133). It is recommended that the entire 167-page Journal be read to show how ill-founded is the Wessely School's "CBT model" of ME/CFS.

In their Closing Remarks, Professors Komaroff and Klimas said: "***Few studies by psychiatrists are presented in this supplement. Many investigators who have argued that CFS is primarily a psychiatric disorder chose not to present their work***" (Clin Inf Dis 1994:18:(Suppl 1):S166-167).

1995

*"These results suggest there is persistence of enterovirus infection in some CFS patients and indicate the presence of distinct novel enterovirus sequences…****Several studies have shown that a significant proportion of patients***

complaining of CFS have markers for enterovirus infection*….From the data presented here…the CFS sequences may indicate the presence of novel enteroviruses…****It is worth noting that the enteroviral sequences obtained from patients <u>without</u> CFS were dissimilar to the sequences obtained from the CFS patients…This may provide corroborating evidence for the presence of a novel type of enterovirus associated with CFS****"* (DN Galbraith, C Nairn and GB Clements. Journal of General Virology 1995:76:1701-1707).

<u>1995</u>

"In the CFS study group, 42% of patients were positive for enteroviral sequences by PCR, compared to only 9% of the comparison group…Enteroviral PCR does, however, if positive, provide evidence for circulating viral sequences, and has been used to show that ***enteroviral specific sequences are present in a significantly greater proportion of CFS patients than other comparison groups****"* (C Nairn et al. Journal of Medical Virology 1995:46:310-313).

<u>1997</u>

"To prove formally that <u>persistence</u> rather than re-infection is occurring, it is necessary to identify a unique feature retained by serial viral isolates from one individual. ***We present here for the first time evidence for enteroviral persistence (in humans with CFS****)…" (*DN Galbraith et al. Journal of General Virology 1997:78:307-312).

<u>1998</u>

*"Recent developments in molecular biology…have revealed a hitherto unrecognised association between enteroviruses and some of the most disabling, chronic and disheartening neurological, cardiac and endocrine diseases…****Persistent infection (by enteroviruses) is associated with ME/CFS****…The difficulty of making a differential diagnosis between ME/CFS and post-polio sequelae cannot be over-emphasised…*(EG Dowsett. Commissioned for the BASEM meeting at the RCGP, 26th April 1998:1-10).

<u>2000</u>

An important paper by Ablashi and Peterson et al suggested that in both multiple sclerosis (MS) and (ME)CFS, HHV-6 reactivation plays a role in the pathogenesis.

"***Two disorders of significant importance, MS and CFS, appear to be associated with HHV-6 infection…the data presented here show that both MS and CFS patients tend to carry a higher rate of HHV-6 infection or reactivation compared to normal controls. This immunological and virological data supports a role of HHV-6 in the symptomatology of these diseases****…Based on biological, immunological and molecular analysis, the data show that HHV-6 isolates from 70% of CFS patients were Variant A…Interestingly, the majority of HHV-6 isolates from MS patients were Variant B…These data demonstrate that the CFS patients exhibited HHV-6 specific immune responses…****Seventy percent of the HHV-6 isolates from CFS patients were Variant A, similar to those reported in AIDS…It has already been shown that active HHV-6 infection in HIV-infected patients enhanced the AIDS disease process. We suspect that the same scenario is occurring in the pathogenesis of MS and CFS****…The immunological data presented here clearly shows a significantly high frequency of HHV-6 reactivation in CFS and MS patients. We postulate that active HHV-6 infection is a major contributory factor in the aetiologies of MS and CFS" (*DV Ablashi, DL Peterson et al. Journal of Clinical Virology 2000:16:179-191).

(HHV-6 is one of eight known members of the human herpesvirus family. It has two variants [A and B]; the A strain is much more pathogenic and infects the immune and central nervous systems. Reactivation in adults has been associated with glandular fever, autoimmune disorders and diseases of the nervous system. Active HHV-6 infections are not found in healthy people without disease associations and reactivation can result in suppression of bone marrow function and inflammation, and can cause damage in tissues such as brain, liver or lungs. HHV-6 has been specifically linked to MS, AIDS and (ME)CFS [Co-Cure MED: 2nd March 2002]. HHV-6 used to be called human B-lymphotropic virus (HBLV); it was discovered in 1986 from

the blood of patients with AIDS. HHV-6 also correlates with 37kDa – the low molecular weight form of RNase L that is known to exist as part of a dysregulated antiviral pathway in ME/CFS patients).

2001

"Over the last decade a wide variety of infectious agents has been associated with CFS by researchers from all over the world. Many of these agents are neurotrophic and have been linked to other diseases involving the central nervous system (CNS)*…Because patients with CFS manifest a wide range of symptoms involving the CNS as shown by abnormalities on brain MRIs, SPECT scans of the brain and results of tilt-table testing, we sought to determine the prevalence of HHV-6, HHV-8, EBV, CMV, Mycoplasma species, Chlamydia species and Coxsackie virus in the spinal fluid of a group of patients with CFS. Although we intended to search mainly for evidence of actively replicating HHV-6, a virus that has been associated by several researchers with this disorder,* ***we found evidence of HHV-8, Chlamydia species, CMV and Coxsackie virus in (50% of patient) samples…It was also surprising to obtain such a relatively high yield of infectious agents on cell free specimens of spinal fluid that had not been centrifuged****"* (Susan Levine. JCFS 2002:9:1/2:41-51).

(HHV-8 is associated with Kaposi's sarcoma and with some B-cell lymphomas).

2003

Nicolson et al showed that multiple co-infections (Mycoplasma, Chlamydia, HHV-6) in blood of chronic fatigue syndrome patients are associated with signs and symptoms: *"****Differences in bacterial and/or viral infections in (ME)CFS patients compared to controls were significant…The results indicate that a large subset of (ME)CFS patients show evidence of bacterial and/or viral infection(s)****, and these infections may contribute to the severity of signs and symptoms found in these patients" (*Nicolson GL et al. APMIS 2003:111(5):557-566).

2003

Seeking to detect and characterise enterovirus RNA in skeletal muscle from patients with (ME)CFS and to compare efficiency of muscle metabolism in enterovirus positive and negative (ME)CFS patients, Lane et al obtained quadriceps biopsy samples from 48 patients with (ME)CFS. Muscle biopsy samples from 20.8% of patients were positive, while 100% of the controls were negative for enterovirus sequences. Lane et al concluded: "*There is an association between abnormal lactate response to exercise, reflecting impaired muscle energy metabolism, and the presence of enterovirus sequences in muscle in a proportion of (ME)CFS patients"* (RJM Lane, LC Archard et al. JNNP 2003:74:1382-1386).

2005

In their presentation to the US Assembly Committee, Drs Dharam Ablashi and Kristin Loomis said:

*"****Reasons to suspect viruses as a cause of CFS and MS****: **In CFS, symptoms wax and wane; antiviral pathways are activated; symptoms are similar to many viral conditions**; geographic outbreaks have been reported;* ***gene expression profiling found genetic variants that reduce antiviral defences.*** *In MS, antiviral pathways are activated; geographic outbreaks have been reported; all demyelinating disorders with known aetiology have been caused by viruses; symptoms wax and wane and worsen with viral infections.*

"Evidence of central nervous system abnormalities in (ME)CFS are similar to those in MS: reduced grey matter volume in bilateral prefrontal cortex; abnormal uptake of acetyl-L carnitine in the prefrontal cortex; enlarged ventricle volumes; increased small punctate lesions on MRI in MS and in a subset of (ME)CFS; fatigue is present in more than 85% of people with MS and in 100% of people with (ME)CFS; reduced information processing speed; memory and cognitive problems".

Ablashi and Loomis pointed out that **an analysis of studies of HHV-6 in (ME)CFS differentiated between active and latent virus, with 83% being positive** (Assessment and Implications of Viruses in Debilitating Fatigue in CFS and MS Patients. Dharam V Ablashi et al. HHV-6 Foundation, Santa Barbara, USA. Submission to Assembly Committee/Ways & Means, Exhibit B1-20, submitted by Annette Whittemore 1st June 2005).

2005

In a review of the role of enteroviruses in (ME)CFS, Chia noted that initial reports of chronic enteroviral infections causing debilitating symptoms in (ME)CFS patients were met with scepticism and largely forgotten, but observations from *in vitro* experiments and from animal models clearly established a state of chronic persistence through the formation of double stranded RNA, similar to findings reported in muscle biopsies of patients with (ME)CFS. Recent evidence not only confirmed the earlier studies, but also clarified the pathogenic role of viral RNA (JKS Chia. Journal of Clinical Pathology 2005:58:1126-1132).

2006

*"We now recognise that the immune system plays a crucial role in the pathogenesis of (ME)CFS…A disruption of the HPA axis has been implicated in the pathogenesis of (ME)CFS…A link between the immune system and the HPA axis has long been established…it is likely that HPA axis dysfunction is not the cause of (ME)CFS, but that it is secondary to the primary pathogenesis. However, once invoked, HPA axis dysfunction may contribute towards the perpetuation of the illness…Stress is known to have a significant modulating effect on the pathogenesis of viral infection (and) the principal means by which this influence occurs is likely to be via the HPA axis…Early beliefs that (ME)CFS may be triggered or caused by a single virus have been shown to be unsubstantiated (and) it is likely that different viruses affect different individuals differently, dependent upon the …immune competence of the individual…**Infections are known to trigger and perpetuate the disease in many cases. Therefore, one valuable approach that has not been widely adopted in the management of (ME)CFS patients is to exhaustively investigate such patients in the hope of identifying evidence for a specific persistent infection** (but in the UK, NICE specifically does not permit such investigations)….**Enteroviruses have been reported to trigger approximately 20% of cases if (ME)CFS…Antibodies to Coxsackie B virus are frequently detected in (ME)CFS patients, and enterovirus protein and RNA occur in the muscle and blood of (ME)CFS patients and their presence has been associated with altered metabolism in the muscle upon exercise in the context of (ME)CFS**".

Kerr et al then go on to provide evidence of other triggers of (ME)CFS which include Parvovirus; *C. pneumoniae*; *C. burnetti;* toxin exposure and vaccination including MMR, pneumovax, influenza, hepatitis B, tetanus, typhoid and poliovirus (LD Devanur, JR Kerr. Journal of Clinical Virology 2006: 37(3):139-150).

2006

Having carried out a prospective cohort study of post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens, the authors concluded: *"**The syndrome was predicted largely by the severity of the acute illness rather than by demographic, psychological or microbiological factors…Importantly, premorbid and intercurrent psychiatric disorder did not show predictive power for post-infective fatigue at any time point…We propose that …neurobiological mechanisms triggered during the severe, acute illness…underpin the persistent symptoms domains of post-infective fatigue syndrome**"* (Ian Hickie et al. BMJ 2006: 333:575).

2006

*"CFS is a poorly-defined medical condition…which, besides severe chronic fatigue as the hallmark symptom, involves inflammatory and immune activation…**The type I interferon antiviral pathway has been repeatedly shown to be activated in peripheral blood mononuclear cells of the most severely afflicted patients…Recently, the levels of this abnormal protein have been significantly correlated to the extent of inflammatory symptoms***

displayed by (ME)CFS patients. *We report here that active double-stranded RNA-dependent kinase (PKR) is expressed and activated in parallel to the presence of the 37 kDa RNase L and to an increase in nitric oxide production by immune cells…**These results suggest that chronic inflammation due to excess nitric oxide production plays a role in (ME)CFS and that the normal resolution of the inflammatory process by NFK-β activation and apoptotic induction is impaired"*** (Marc Fremont, Kenny De Meirleir et al. JCFS 2006:13:4:17-28).

2006

"(ME)CFS is associated with objective underlying biological abnormalities, particularly involving the nervous and immune system. ***Most studies have found that active infection with HHV-6 – a neurotropic, gliotropic and immunotropic virus – is present more often in patients with (ME)CFS than in healthy control subjects****…Moreover, HHV-6 has been associated with many of the neurological and immunological findings in patients with (ME)CFS"* Anthony L Komaroff. Journal of Clinical Virology 2006:37:S1:S39-S46.

2007

*"**Research studies have identified various features relevant to the pathogenesis of CFS/ME such as viral infection, immune abnormalities and immune activation, exposure to toxins, chemicals and pesticides, stress, hypotension…and neuroendocrine dysfunction….Various viruses have been shown to play a triggering or perpetuating role, or both, in this complex disease….The role of enterovirus infection as a trigger and perpetuating factor in CFS/ME has been recognised for decades****…The importance of gastrointestinal symptoms in CFS/ME and the known ability of enteroviruses to cause gastrointestinal infections led John and Andrew Chia to study the role of enterovirus infection in the stomach of CFS/ME patients…They describe a systematic study of enterovirus infection in the stomach of 165 CFS/ME patients, demonstrating a detection rate of enterovirus VP1 protein in 82% of patients…the possibility of an EV outbreak…seems unlikely, as these patients developed their diseases at different times over a 20 year period"* (Jonathan R Kerr. Editorial. J Clin Pathol 14th September 2007. Epub ahead of print).

2007

"*Since most (ME)CFS patients have persistent or intermittent gastrointestinal (GI) symptoms, the presence of viral capsid protein 1 (VP1), enterovirus RNA and culturable virus in the stomach biopsy specimens of patients with (ME)CFS was evaluated…Our recent analysis of 200 patients suggests that… enteroviruses may be the causative agents in more than half of the patients…At the time of oesophagogastroduodenoscopy, the majority of patients had mild, focal inflammation in the antrum…95% of biopsy specimens had microscopic evidence of mild chronic inflammation…82% of biopsy specimens stained positive for VP1 within parietal cells, whereas 20% of the controls stained positive…An estimated 80-90% of our 1,400 (ME)CFS patients have recurring gastrointestinal symptoms of varying severity, and epigastric and/or lower quadrant tenderness by examination…Finding enterovirus protein in 82% of stomach biopsy samples seems to correlate with the high percentage of (ME)CFS patients with GI complaints…Interestingly, the intensity of VP1 staining of the stomach biopsy correlated inversely with functional capacity…A significant subset of (ME)CFS patients may have a chronic, disseminated, non-cytolytic form of enteroviral infection which can lead to diffuse symptomatology without true organ damage" (*Chia JK, Chia AY. J Clin Pathol 13th September 2007 Epub ahead of print).

2009

As mentioned above, researchers from the Enterovirus Research Laboratory, Department of Pathology and Microbiology, University of Nebraska Medical Centre wrote a specially-commissioned explanatory article for the UK charity Invest in ME, in which they stated that human enteroviruses were not generally thought to persist in the host after an acute infection, but they had discovered that Coxsackie B viruses can naturally delete sequence from the 5' end of the RNA genome, and that this results in long-term viral persistence, and that *"This previously unknown and unsuspected aspect of enterovirus replication provides an explanation for previous*

*reports of enteroviral RNA detected in diseased tissue in the apparent absence of infectious virus particles" (*S Tracy and NM Chapman. Journal of IiME 2009:3:1). (http://www.investinme.org/Documents/Journals/Journal%20of%20IiME%20Vol%203%20Issue%201.pdf).

In her lecture in November 2009 at the University of Miami, Professor Nancy Klimas said about viruses and ME/CFS that much of the research at Miami and internationally found that the viruses studied all have several things in common: they infect cells of the immune system and the neurological system; they are capable of causing latent infections and they can reactivate under certain conditions.

She also said that their early work at Miami in the late 1980s (published in the Journal of Clinical Microbiology in 1989) showed that ME/CFS patients had immune activation and poor anti-viral cell function. She then went on to discuss the importance of the findings of the retrovirus XMRV (evidence of which was published in Science on 8th October 2009 -- see below), saying that it was *"very impressive work"*. She continued: "*This Science paper was amazing for a number of reasons. First, this team had put together such strong science that they could go for a Science paper. Science is like the Mecca of publication. If you get your stuff in Science, that's the best place you could possibly (get it published). And they don't take just anything and they sure, sure, sure don't take anything unless it's extremely well done, validated and tested out. So they took this paper – they not only took it, they put it in Science Express. They thought it was so important, they published on a very fast track…The way (the researchers at the Whittemore Peterson Institute) looked is very sophisticated…They then tried to find (the virus) in all these other ways…they looked from a whole different angle. Still found it. Backed up and looked from another angle. Still found it…they had five different kinds of ways they looked for this virus. And they were able to find the virus. That's why Science was so impressed…It is a virus that can infect tissues that aren't white blood cells…**We've always thought something like that has to go on in (ME)CFS because you all have some neuro-inflammation. Your brain has a low grade level of inflammation. And you have some inflammation in the tissues that make hormones, particularly in the hypothalamic-pituitary-axis. And this is a virus that infects that type of tissue**…It's pretty impressive that out of 101 (ME)CFS cases defined by clinical case definition or a research case definition that they found 99 with the virus…And, oh, by the way, we have a biomarker. Not a small deal. A biomarker – the virus itself. No better biomarker than something that's clearly, tightly associated with an illness…So the conclusion, it really is a big thing. It's a big thing…That work we were already doing plays right into this. All the genomics work and all the immunology work. This is all critical to the better understanding of this illness and how this virus plays into it"* (with grateful acknowledgement to PANDORA and http://aboutmecfs.org/Rsrch/XMRVKlimas.aspx and http://aboutmecfs.org/Rsrch/XMRVKlimasII.aspx).

The Whittemore-Peterson Institute's study that found the new human retrovirus XMRV was listed as one of the top 100 scientific discoveries in 2009 in Discovery magazine's January 2010 issue (Co-Cure NOT: 30th December 2009).

The role of viruses in ME/CFS

For decades it has been known and shown that viruses play a role in ME/CFS. Now there is evidence of a direct link with a virus that disables the immune system, thus allowing numerous latent viruses to re-activate, which may result in the protean symptomatology.

In relation to "CFS", the most-studied viruses have been the Epstein-Barr Virus (EBV) and the Human Herpes Virus-6 (HHV-6).

In relation to "pure" ME, the most studied viruses (and for which there is extensive evidence) have been the enteroviruses, usually Coxsackie B (CBV).

There is increasing awareness that the dysregulated immune system that is a hall-mark of ME/CFS allows multiple latent viruses and microbial agents to become reactivated (Co-Cure NOT:12th November 2009).

Moreover, recent research has shown that even viruses which were hitherto believed not to persist after an acute infectious episode are capable of long-term viral persistence.

Dr John Chia, an infectious diseases specialist from Torrance, California, who specialises in ME/CFS, is on record: *"I believe that the main reason (ME)CFS patients are symptomatic is due to continuing inflammatory response toward viruses living within the cells, enteroviruses in most of the cases I see. We have clearly documented certain enterovirus infections triggering autoimmune responses in some patients…**Can you imagine how we would feel if there are viruses surviving in our muscles, brains, hearts and gastrointestinal tracts triggering ongoing immune responses?"*** (http://aboutmecfs.org/blog/?p=865).

The CFIDS Chronicle (Research Update, Summer 1993) explained viruses and retroviruses as follows:

"*A virus is a microscopic organism that lives within the cells of another living organism. Viruses cause disease at the most basic level, by damaging the cells of living things. By themselves, viruses are lifeless particles incapable of reproduction, but once they enter the cell of another living thing they become active organisms that can multiply hundreds of times.*

"Viruses are comprised of two parts – a core of either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) and a protective envelope of protein. RNA viruses are smaller than DNA viruses and sometimes contain a special enzyme called reverse transcriptase which allows them to convert RNA to DNA. These specialised viruses are known as retroviruses and have a unique ability to merge with the host's own genetic material.

"Retroviruses have the unique ability to replicate themselves by (i) making a double-stranded DNA copy called a 'pro-virus' once they enter living cells. Pro-viruses integrate themselves into the human chromosome and become part of the host's genetic code (ii) alter the host's immune response by evading detection as a 'hidden invader' (iii) remain hidden and latent, spliced within the host's DNA, for long periods of time. Retroviruses are known to be potent stimulators of cytokines".

On 8th October 2009 the premier journal Science published a paper online showing a direct link between a retrovirus and ME/CFS (Detection of infectious retrovirus XMRV, in blood cells of patients with chronic fatigue syndrome. Lombardi VC, Ruscetti FW, Peterson DL, Silverman RH, Mikovits JA et al) which caused global reverberations (see below).

However, this was not the first time that a retrovirus had been associated with ME/CFS.

The first time was in 1991 when, using polymerase chain reaction and in situ hybridisation, Dr Elaine De Freitas, a virologist at the Wistar Institute, Philadelphia (which is America's oldest independent institution devoted to biological research) and Drs Daniel Peterson, Paul Cheney, David Bell et al found such an association (Retroviral sequences related to human T-lymphotropic virus type II in patients with chronic fatigue immune dysfunction syndrome. Proc Natl Acad Sci USA 1991:88:2922-2926). It is notable that co-author Hilary Koprowski is a distinguished virologist and Professor Laureate who was Director of the Wistar Institute from 1957-1991; he is a member of the US National Academy of Sciences and is Director of the Centre for Neurovirology at Thomas Jefferson University.

Before publication, the findings were presented on 4th September 1990 by Elaine De Freitas at the 11th International Congress of Neuropathology in Kyoto, Japan.

Ten days later, on 14th September 1990 Dr Peter White (as he then was) and other members of the Wessely School dismissed the findings: *"in the vast majority of CFS cases there is a psychological component. About 75% of CFS sufferers are clinically depressed, according to Peter White, senior lecturer in the department of psychiatric medicine at St Bartholomew's Hospital in London.* ***White said he believes depression is often a cause, rather than a consequence, of CFS…Les Borysiewicz, a clinical virologist at Addenbrookes Hospital in Cambridge*** (who, as noted above, is now Chief Executive of the MRC, having succeeded Professor Colin Blakemore)

(said) 'Whatever causes CFS, it isn't the virus itself'*…Anthony Clare, psychiatrist and medical director of St Patrick's Hospital in Dublin* (now deceased), *pointed out that…there have been many 'fatigue' diseases with shifting causes: 'Neurasthenia, food allergies, now viruses. Some people would always rather have a disease that might kill them than a syndrome they have to live with' "* (Science 1990:249:4974:1240).

In their PNAS article that was published in April 1991, De Freitas et al noted that chronic fatigue immune dysfunction syndrome (CFIDS) *"may be related or identical to myalgic encephalomyelitis"* and examined adult and paediatric CFIDS patients for evidence of human retroviruses (HTLV types I and II). As the CFIDS Chronicle article noted, the Wistar team looked at the peripheral blood DNA to see if they could find messenger RNA (mRNA) encoding for a viral segment of the HTLV-II virus.

At that time, known human retroviruses were the human immunodeficiency viruses 1 and 2 (HIV-1 and HIV-2) which are known to cause AIDS, and human T-lymphotropic viruses HTLV-I which causes lymphoma and HTLV-II which causes leukaemia (Hunter-Hopkins ME-Letter, October 2009). The four segments of the HTLV-II virus are referred to as the *env*, *gag*, *pol* and *tax*.

After a two-year study, De Freitas et al provided evidence for HTLV-II-like infection of blood cells from CFIDS patients (and also to a lesser extent from people closely associated with them). This evidence was further substantiated by patient reactivity to proteins with the molecular weights reported for HTLV-I and HTLV-II antigens.

In their article, De Freitas et al said: "*The frequency of these antibodies in CFIDS patients compared with healthy non-contact controls suggests exposure / infection with an HTLV-like agent rare in healthy non-contact people".*

Whilst none of the CFIDS patients' blood samples contained detectable HTLV-I gag sequences, DNA from at least two separate bleedings was positive for the HTLV-II gag subregion in 83% of adult and 72% of paediatric CFIDS patients, and the authors pointed out that *"similar frequencies of PBMCs* (peripheral blood mononuclear cells) *expressing retroviral mRNA have been reported for HIV-infected individuals…The clinical histories of these CFIDS patients do not reveal behavioural or genetic factors usually associated with retroviral infection. Yet our data suggest that not only are these HTLV-II-like genes and HTLV-reactive antibodies associated with CFIDS in patients but that samples from a significant proportion of their non-sexual contacts are positive".*

De Freitas et al were careful to emphasise that "*Although our data support an association between an HTLV-like agent and CFIDS, we cannot, as yet, define the agent's role in the disease process. It may be a secondary infection to which immunologically compromised patients are susceptible. Alternatively, it may be one of two viruses that, when co-infecting the same haematopoetic cells, induce immune dysfunction".*

Following the Wistar findings, researchers at the US Centres for Disease Control (CDC) allegedly attempted to replicate De Freitas' work but failed to do so; this was suggested to be because certain scientists appeared eager to discount any possibility of a retroviral association with CFIDS. De Freitas defended her work and insisted that the CDC investigators had modified her assays, with the result that her work could not be replicated by the CDC. It is known that attempts to replicate De Freitas' work differed substantially from her own work in a number of ways, including the clinical definition of patients studied; uniform failure to use a "hot start" procedure with the PCR assay to maximise the efficiency of the PCR reaction, and the use of experimental conditions for the PCR assay that differed significantly from those used by De Freitas et al (Co-Cure RES: 6th March 2002).

De Freitas was publicly discredited; her research funding was discontinued and her research abandoned; she was subjected to what appeared to be attempts to destroy her professional reputation. Commenting on the subsequent discovery of XMRV (see below), ME/CFS expert Dr Paul Cheney of The Cheney Clinic was unambiguous: "*Her work was unfortunately assaulted by the CDC. Her proposal to fly to the CDC in Atlanta to physically run the assays side by side with the CDC scientists was dismissed by the CDC"* (http://cheneyclinic.com/a-retrovirus-called-xmrv-is-linked-to-cfs/538).

In August 1991, together with co-author Brendan Hilliard, Elaine De Freitas applied for a world patent that was subsequently issued in April 1992. Detailed information has been provided by Dr Alan Cocchetto, Medical Director of The National CFIDS Association (http://www.ncf-net.org/forum/revelations.html). Cocchetto is clear: "*the contents of this paper have major implications due to the depth and scientific quality of the work…The entire patent is approximately 40 pages. If the NIH ignored the depth of this work… then the NIH dropped the ball on this one and should be held accountable.* ***The inventors even state: 'The ability to screen blood samples infected by CAV*** **(CFIDS-associated virus)** ***enables producers and distributors of blood products, eg. the American Red Cross, to identify and discard donated blood…intended for use in transfusions…If unscreened, the use of such blood and blood-derived products could contribute to the spread of CFIDS'****. The inventors reveal: 'Neither HTLV-I, II, nor HIV virions have ever been found inside mitochondria…****the positive results support the possibility that this CAV is capable of casual transmission to non-infected persons'.*** *If the NIH ignored this last comment, then something is dramatically wrong with the agency that is supposed to protect and safeguard the welfare of the citizens of the United States.* ***Again, the implications here are just staggering****…The only conclusion that can be reached is that this work is very thorough and extensive. It has been funded by the NIH….Any retrovirus that can invade the mitochondria directly indicates trouble. As far as I'm concerned, there needs to be a criminal investigation of the NIH regarding why they refused to fund upon submission of all this data".*

It has been said that De Freitas' reputation was intentionally destroyed because her research did not support the theory that (ME)CFS is a psychoneurosis, and that her public discrediting caused others to fear following up her work (Co-Cure;NOT: 16th October 2009).

As Neenyah Ostrom commented: "*CFS and AIDS do not exist primarily in a scientific environment: they exist, for the most part, in an extremely political environment"* (New York Native, 28th November 1994).

There undoubtedly seems to be collaboration about policy concerning ME/CFS between the UK Wessely School and Dr William (Bill) Reeves, Principal Investigator of the CDC's CFS research programme, who is held in the same disregard in the US as Professor Simon Wessely is held in the UK (see below).

Regarding blood donation by people with ME/CFS, it is a matter of record that in reply to a letter dated 21st December 1991 from the late Joan Irvine, on 16th January 1992 Dr George Rutherford, Chief of the Infectious Diseases Branch of the US Department of Health and Human Services, replied to her query about blood donation by people with (ME)CFS:

"*…a number of researchers have postulated that it may be caused by an infectious agent or agents, such as a virus…Based on our knowledge of infectious diseases of the immune system, it is not impossible that one or more of these suggested agents might potentially be able to be transmitted through blood-to-blood contact, as occurs in blood transfusions…I think that it is best to await further research findings before resuming blood donation".*

Also on 16th January 1992, the same Dr William Reeves of the CDC wrote to Joan Irvine about the same issue:

"*…since on-going research indicates an infectious agent may be involved in some cases of CFS it would seem prudent to refrain from donating blood until this issue is resolved"* (http://www.cfs-news.org/joan.htm).

As noted above, people in the UK with ME have been **permanently** excluded from donating blood since at least 1989 (Guidelines for the Blood Transfusion Service in the UK, 1989: 5.4; 5.42; 5.43; 5.44; 5.410).

This was subsequently upheld by the Parliamentary Under Secretary of State The Lord Warner, who confirmed in writing on 11th February 2004 in a letter to the Countess of Mar that people with ME/CFS are not permitted to be blood donors. Lord Warner was unambiguous: *"We have checked with the National Blood Service and they have provided the following information. The NBS guidelines on donor selection on ME refer to those on Post Viral Fatigue Syndrome. The Guidance is: defer from blood donation until recovery. The underlying logic*

is that this condition is possibly viral and therefore the NBS cannot accept the risk of possible transmission by blood. Since the condition is very variable and sometimes prolonged, it could become a lifetime ban in any particular case. I have copied this letter to the House (of Lords) library".

Given the (re)-discovery of a direct link between a retrovirus and ME/CFS, the importance of this cannot be over-stated.

Notably, those with a behavioural disorder are not prevented from donating blood.

XMRV (retrovirus associated with ME/CFS)

As mentioned above, in October 2009 the journal Science published a paper by collaborators from the Whittemore Peterson Institute, the US National Cancer Institute and The Cleveland Clinic that demonstrated a direct link between the retrovirus XMRV and ME/CFS (Science: 8th October 2009:10.1126/science.1179052).

XMRV stands for xenotropic murine leukaemia virus-related virus (xenotropic meaning a virus that can grow in the cells of a species foreign to the normal host species, ie. a virus that is capable of growing in a foreign environment).

XMRV is a member of the same family of retroviruses as the AIDS virus. A retrovirus inserts itself into the host's genetic material by copying its genetic code into the DNA of the host by using RNA and once there, it stays for the life of the host.

It is understood that Mikovits' discovery was deemed to be of such magnitude by the world's most prestigious science journal that the authors' paper (which was submitted on 6th May 2009) was sent to three times the customary number of referees prior to acceptance and publication.

Shortly before the Mikovits et al paper was published, on 24th September 2009 the Whittemore Peterson Institute (WPI) announced that Dr Mikovits and collaborator Dr Jonathan Kerr of St George's, London, had been awarded a $1.6 million five-year grant by the US National Institute of Allergy and Infectious Diseases for research into the causes and diagnosis of neuro-immune diseases (http://www.wpinstitute.org/news/news_current.html). The Project Number is 1R01A1078234-01A2 and the description provided by the applicants says:

"CFS is a complex disease estimated to affect between 0.5% - 2% of the population of the Western world. ***Its pathogenesis is thought to involve both inherited and environmental (including viral) components, as with other chronic inflammatory diseases such as multiple sclerosis…Consistent with this chronic inflammatory context, CFS patients are known to have a shortened life-span and are at risk for developing lymphoma.*** *We hypothesise that chronic inflammatory stimulation from active and recurrent infections of multiple viruses on a susceptible host genetic background leads to the pathogenesis characterised by CFS. The overall goal of this research project is to define those viral and host parameters…The proposed research will provide significant insight into the disease mechanism of Chronic Fatigue Syndrome so accurate testing and specific treatments can be developed with a goal of curing the disease and preventing life-threatening complications"* (Co-Cure NOT:RES:21st October 2009).

It is worth noting that three days before the Mikovits et al article was published in Science, on 5th October 2009 Professor Peter White in collaboration with Dr Bill Reeves of the CDC published a paper in which they described endophenotypes of CFS (which White talked about in his presentation at Bergen on 20th October 2009 – see below). According to Wikipedia, "endophenotype" is a psychiatric concept, the purpose of which is to divide behavioural symptoms into separate phenotypes with clear genetic connections. The relevance of this to the neuro-immune disease ME/CFS has not been explained, but White and Reeves et al concluded:

"The data do not support the current perception that CFS represents a unique homogeneous disease" (Population Health Metrics 2009:7:17doi:10.1186/1478-7954-7-17).

In contrast, in their article in Science Mikovits et al deal with science, not speculation:

"Chronic fatigue syndrome (CFS) is a debilitating disease of unknown aetiology that is estimated to affect 17 million people worldwide.

"Studying peripheral blood mononuclear cells (PBMCs) from CFS patients, we identified DNA from a human gammaretrovirus (XMRV) in 68 of 101 patient (67%) compared to 8 of 218 (3.7%) healthy controls" (gammaretroviruses are known to cause cancer, immunological and neurological diseases in animals).

"Cell culture experiments revealed that patient-derived XMRV is infectious and that both cell-associated and cell-free transmission of the virus are possible".

"CFS affects multiple organ systems in the body. Patients with CFS display abnormalities in immune system function, often including chronic activation of the innate immune system and a deficiency in natural killer (NK) cell activity. A number of viruses, including ubiquitous herpesviruses and enteroviruses have been implicated as possible environmental triggers of CFS. Patients with CFS often have active β herpesevirus infections, suggesting an underlying immune deficiency.

"The recent discovery of a gammaretrovirus, XMRV, in the tumour tissue of a subset of prostate cancer patients prompted us to test whether XMRV might be associated with CFS. Both of these disorders, XMRV-positive prostate cancer and CFS, have been linked to alterations in the antiviral enzyme RNase L" (as noted above, RNase L is the terminal enzyme in the 2-5A synthetase/RNase L antiviral pathway in the immune system. It plays an essential role in the elimination of viral mRNA. Deregulation of this pathway in subsets of ME/CFS patients has been reported extensively in the scientific literature. In ME/CFS, a wide spectrum of cleavage of RNase L is observed, a phenomenon also seen in MS patients, and such altered RNase L activity profoundly affects cellular physiology, including apoptosis or programmed cell death – Dr Neil Abbot: Co-Cure RES:MED: 16th October 2009).

"Neurological maladies and immune dysfunction with inflammatory cytokine and chemokine up-regulation are some of the most commonly reported features associated with CFS…The presence of infectious XMRV in lymphocytes may account for some of these observations of altered immune responsiveness and neurological function in CFS patients.

"In summary, we have discovered a highly significant association between the XMRV retrovirus and CFS.

"This observation raises several important questions. Is XMRV infection a causal factor in the pathogenesis of CFS or a passenger virus in the immunosuppressed CFS patient population?…Conceivably these viruses could be co-factors in pathogenesis, as is the case for HIV-mediated disease, where co-infecting pathogens play an important role. Patients with CFS have an elevated risk of cancer.

"It is worth noting that 3.7% of the healthy donors in our study tested positive for XMRV sequences. This suggests that several million Americans may be infected with a retrovirus of as yet unknown pathogenic potential".

The published supplementary material confirms: "*Banked samples were selected for this study from patients fulfilling the 1994 CDC Fukuda Criteria for Chronic Fatigue Syndrome and the 2003 Canadian Consensus Criteria for Chronic fatigue syndrome / myalgic encephalomyelitis and presenting with severe disability".*

Commenting on this discovery, Professor John Coffin Coffin from the Department of Molecular Microbiology, Tufts University, Boston, a National Academy of Sciences member and expert retrovirologist who edited the 1997 reference book "Retroviruses" (proclaimed as "outstanding" by the New England Journal of Medicine) who was not involved with the study and who was at first highly sceptical but who

was converted by the WPI team's independent lines of evidence, together with Jonathan Stoye from the UK National Institute for Medical Research, Mill Hill, London, (who is Head of the Virology Division at the Medical Research Council), stated:

"*Although chronic inflammation is often found in these patients, no infectious or toxic agent has been clearly implicated in this disease….Chronic fatigue syndrome is not the first human disease to which XMRV has been linked. The virus was first described about three years ago in a few prostate cancer patients and recently detected in nearly a quarter of all prostate cancer biopsies. It has been isolated from both prostate cancer and chronic fatigue syndrome patients, and is similar to a group of endogenous murine leukaemia viruses (MLVs)…There is more than 90% DNA sequence identity between XMRV and xenotropic MLV, and their biological properties are virtually indistinguishable.*

"There are several lines of evidence that transmission happened in the outside world and was not a laboratory contaminant. One is that XMRVs from disparate locations and from both chronic fatigue syndrsome and prostate cancer patients are nearly identical…Other evidence includes the presence of XMRV and high amounts of antibodies to XMRV and other MLVs in chronic fatigue syndrome and prostate cancer patients.

"Two characteristics of XMRV are particularly noteworthy. One is the near genetic identity of isolates from different diseases and from individuals in different parts of the United States. The two most distantly related genomes sequenced to date differ by fewer than 30 out of about 8,000 nucleotides. Thus, all of the XMRV isolates are more similar to each other than are the genomes isolated from any one individual infected with the human immunodeficiency virus.

"Another notable feature of XMRV is that the frequency of infection in nondiseased controls is remarkably high.

"If these figures are borne out in larger studies, it would mean that perhaps 10 million people in the United States and hundreds of millions worldwide are infected with a virus whose pathogenic potential for humans is still unknown" (http://tinyurl.com/yerdtba).

Announcing their groundbreaking discovery, a press release by R&R Partners on behalf of the Whittemore Peterson Institute said: "***Since the original Science paper was submitted, we have continued to refine our test for XMRV and have surprisingly found that 95% ME/CFS samples tested positive for XMRV antibodies in the plasma. 'This finding clearly points to the retrovirus as a significant contributing factor in this illness'*** *said Judy Mikovits, director of research for WPI.* ***This landmark study was the first to isolate XMRV particles from the blood and show that it can be transmitted between blood cells. Researchers have confirmed that this retrovirus is transmitted through body fluids and is not airborne"*** (http://www.wpinstitute.org/xmrv/docs/wpi_pressrel_100809.pdf).

Commenting on this further information, ME/CFS expert Dr Paul Cheney said: "***The finding of antibody or active virus in 95% of CFS and 4% of controls is a result that argues for causality, in my opinion….This retrovirus could easily …induce all manner of pathogens as seen in CFS (and) could corrupt the gut ecology …observed in CFS and lead to environmental illness as well. Time will tell, but I think Dr Mikovits is right to suspect causality***" (http://cheneyclinic.com/a-retrovirus-called-xmrv-is-linked-to-cfs/583).

On the day that the news broke of the XMRV link with ME/CFS, it was widely reported; prominent sources included AFP; Reuters; Wall Street Journal; Washington Post; New York Times; Nature; Scientific American; New Scientist; NIH News; Science News; NCI Press Release; Scientist, and many national newspapers such as the UK's Daily Telegraph and The Independent.

The Wall Street Journal quoted Judy Mikovits as saying that the XMRV virus creates an underlying immune deficiency which might make people vulnerable to a range of diseases, and it continued: *"Although Thursday's scientific paper doesn't demonstrate conclusively that XMRV is the cause of CFS, additional unpublished data make it a very strong possibility…****'Just like you cannot have AIDS without HIV, I believe you won't be able to find a case of CFS without XMRV' Dr Mikovits said****. …Dr Mikovits also said they also found XMRV in people with autism, atypical multiple sclerosis and fibromyalgia…Robert Silverman, a professor at the Cleveland Clinic*

Lerner Research Institute who is one of the co-authors of the study and one of the discoverers of the XMRV virus, said 'in most cases, people's immune systems are probably able to control the virus'….Researchers are already starting to test anti-retroviral therapies developed for AIDS to see if they are effective against XMRV".

AFP (Agence France Presse) quoted Mikovit's co-author Francis Ruscetti of the Laboratory of Experimental Immunology at the National Cancer Institute: *"These compelling data allow the development of a hypothesis concerning a cause of this complex and misunderstood disease, since retroviruses are a known cause of neurodegenerative diseases and cancer in man".* The AFP report continued: *"Retroviruses like XMRV have also been shown to activate a number of other latent viruses. This could explain why so many different viruses…have been associated with CFS".*

The NIH National Cancer Institute's press release ("Consortium of Researchers Discover Retroviral Link to Chronic Fatigue Syndrome") said: "*Scientists have discovered a potential retrovirus link to chronic fatigue syndrome….**'We now have evidence that a retrovirus named XMRV is frequently present in the blood of patients with CFS. This discovery could be a major step in the discovery of vital treatment options for millions of patients'** said Judy Mikovits, leader of the team that discovered this association….The virus, XMRV, was first identified by Robert H Silverman, professor in the Department of Cancer Biology at the Cleveland Lerner Research Institute…**The research team not only found that blood cells contained XMRV but also expressed XMRV proteins at high levels and produced infectious viral particles**…These results were also supported by the observation of retrovirus particles in patient samples when examined using transmission electron microscopy. The data demonstrate the first direct isolation of infectious XMRV from humans….**Retroviruses like XMRV have also been shown to activate a number of other latent viruses. This could explain why so many different viruses…have been associated with CFS**. Dan Peterson, medical director of WPI, added: **'Patients with CFS deal with a myriad of health issues as their quality of life declines. I'm excited about the possibility of providing patients who are positive for XMRV (with) a definite diagnosis and, hopefully very soon, a range of effective treatment options'** " (http://www.cancer.gov/newscenter/pressreleases/CFSxmrv).

Science News pointed out: ***"The researchers also show that the retrovirus can infect human immune cells…'This is a very striking association – two thirds of the patients'** says John Coffin, a virologist at Tufts University in Boston….**Mikovits asserts that the retroviral infection might result in an immune deficiency that leads to chronic fatigue symptoms. Retroviruses are known to attack the immune system, with HIV being the best-known example. In this study, researchers showed that XMRV infected immune cells in the blood…Retroviruses can awaken latent viruses already in cells. It is possible that symptoms are caused not by XMRV but by other viruses that it activates"**.*

The Scientific American noted: ***"Chronic fatigue…is a misnomer. The syndrome often has more to do with immune system abnormalities than pervasive tiredness**…XMRV has recently been linked to strong cases of prostate cancer. Like CFS, this cancer involves changes in an antiviral enzyme (RNase L)…To find the virus, Mikovits and her team studied documented cases, such as CFS outbreaks in a symphony orchestra in North Carolina and in Incline Village, Nevada. '**We found the virus in the same proportion in every outbreak',** she says….**Experiments in Mikovits' lab proved that the retrovirus can be transmitted via blood by infecting healthy cells drawn from volunteers with material from XMRV-positive CFS patients"**.*

Ewen Callaway (New Scientist) also quoted Mikovits as confirming that her team had found antibodies against XMRV in 95% of nearly 300 patients they tested, but these further results have yet to be published in a journal. Antibodies are a more sensitive test than looking for viral genes, as they pick up people who have had XMRV in the past, not just those who still have it. Callaway noted that Mikovits also pointed out a very significant fact: not only do characteristics of the virus match the symptoms of (ME)CFS, but **viruses related to XMRV can cause blood vessels around the body to leak, a common symptom of (ME)CFS**. Quoting Jonathan Kerr of St George's University of London, Callaway said: " *'XMRV infection of natural killer cells may affect their function…This does fit' "*. Callaway continued: "That sentiment is echoed by John Coffin…*'This looks like a very, very interesting start', he says. 'It's not impossible that this could cause a disease with neurological and immunological consequences' "*.

The UK's Daily Telegraph proclaimed on 9th October 2009: "*Most cases of chronic fatigue syndrome or ME may be linked to a virus, according to research that could lead to the first drug treatments for the disorder that affects millions around the world…Symptoms…can be as disabling as multiple sclerosis…Dr Mikovits' team said further research must now determine whether XMRV directly causes CFS, is just a passenger virus in the suppressed immune systems of sufferers or a pathogen that acts in concert with other viruses that have been implicated in the disorder by previous research*".

Also on 9th October 2009, The Independent's Science Editor, Steve Connor, reported the ground-breaking research on the front page. He said that Dr Judy Mikovits, senior author of the study and Director of Research at the Whittemore Peterson Institute in Reno, Nevada, had confirmed that *"further blood tests have revealed that more than 95% of the patients with the syndrome have antibodies to the virus, indicating that they have been infected with XMRV…'With these numbers, I would say yes, we have found the cause of chronic fatigue syndrome. We also have data showing that the virus attacks the human immune system' "*. **Connor reported that Dr Mikovits is testing a further 500 blood samples gathered from chronic fatigue syndrome patients diagnosed in London. " *'The same percentages are holding up' she said*".**

Of note is that the UK's NHS Knowledge Service (for several years the NHS has persisted in including ME/CFS in its mental health minimum dataset despite frequent requests to categorise it correctly) said: "*CFS affects a range of organs in the body, and patients show abnormal immune system function…one theory is that certain viruses trigger the disease…Overall, samples from the people with CFS were 54 times as likely to contain viral sequences as samples from healthy controls*" (http://www.nhs.uk/news/2009/10October/Pages/Does-a-virus-cause-ME.aspx).

On 8th October 2009 Hillary Johnson, outspoken author of "Osler's Webb: Inside the Labyrinth of the Chronic Fatigue Syndrome Epidemic" (Crown Publishing Inc, New York, 1996), was blunt: "*A generation of quacks and sub-par investigators will be in retreat…The real scientists have arrived and they'll be studying XMRV-associated neuro-immune disease, (i.e.) XAND….the Whittemore Peterson Institute and its collaborators have turned a 20-year crime story back into a science story.* ***Mikovits found XMRV in a sample of frozen blood that had been saved by Dan Peterson as long ago as 1984. The blood happened to have been drawn from a patient who went on to die of mantle cell lymphoma, another disease XMRV is suspected of causing…****the failure of the Centres for Disease Control to respond professionally and rationally when presented with a novel retrovirus in patients and their close contacts in 1991 by Elaine De Freitas needs to be revisited immediately…We've monitored the agency's wilful ignorance of – indeed, their extreme hostility to – the science in this field….if it turns out that their failure to replicate Elaine de Freitas' findings of a novel retrovirus in this disease, followed by their attempt to destroy her professional reputation, was purposeful, then…the CDC is as much a crime scene as it is a federal science agency.* ***How could our government and the governments of other nations dismiss and then ignore millions who suffered from 'an infectious disease of the brain' as Hilary Koprowski of the Wistar Institute called it publicly in 1992. Koprowski was an expert in neurological diseases – he knew one when he saw one…****they will talk about the dangers of scientific bias and the near-criminal manner in which a disease could be defined, for so long and in spite of so much contrary evidence – as a personality disorder…****The years of our lives during which thousands of research papers were written by psychiatrists purporting to explain away a life-destroying disease with discussions of personality disorders, exercise and activity phobia, malingering, hysteria, sexual abuse, school phobia, attention-seeking behaviour must be respected (and) the papers saved for posterity. Princeton English professor Elaine Showalter's book equating this disease with fantasies of alien abduction probably deserves its own shelf in this pantheon of the grotesque…All these works will be examined, in time, by researchers who seek to understand the human capacity for delusion, ignorance and greed***" (http://www.oslersweb.com/blog.htm?post=638469).

Particularly notable was the BBC's reporting of the comments of Tony Britton, the (lay) Publicity Manager at the UK ME Association: *"This is fascinating work, but it doesn't conclusively prove a link between the XMRV virus and chronic fatigue syndrome or ME"*, a statement that should be compared with what was published in Science: "*we have discovered a highly significant association between the XMRV retrovirus and CFS"* and with the WPI press release: "*This finding clearly points to the retrovirus as a significant contributing factor in this illness".*

It is regrettable that the UK ME Association's Publicity Manager seems not to distinguish between proving a conclusive cause and proving a direct link, a link that certainly satisfied the many prestigious referees who advised the journal Science.

It also satisfied Richard T Ellison III, Professor of Medicine, Molecular Genetics and Microbiology in the Division of Infectious Diseases and Immunology at the University of Massachusetts Medical School (Deputy Editor of Journal Watch Infectious Diseases since 1988), who commented: *"**These studies provide clear evidence that active XMRV infection occurs in many CFS patients**"* (Co-Cure RES: 22nd October 2009).

Moreover, as Hillary Johnson reported in the New York Times on 21st October 2009, Judy Mikovits had worked for the National Cancer Institute for 22 years and she was impressed that Dan Peterson *"had built an extraordinary repository of more than 8,000 chronic fatigue syndrome tissue samples going back as far as 1984…**What (Mikovits) found was live, or replicating, XMRV in both frozen and fresh blood and plasma, as well as saliva. She has found the virus in samples going back to 1984 and in nearly all the patients who developed cancer.** She expects the positivity rate will be close to 100% in the disease. **'It's amazing to me that anyone could look at these patients and not see that this is an infectious disease that has ruined lives,' Dr Mikovits said**. She has also given the disease a properly scientific new name: X-associated neuroimmune disease (XAND)".*

On 20th October 2009 Judy Mikovits herself was interviewed; she said: ***"John Coffin is a member of the US National Academy of Sciences. No greater authority on these viruses exists. Three members of the US National Academy of Sciences reviewed this work and all are convinced of the science…they are convinced of the infection and the public health risk**"* (http://merutt.wordpress.com/tag/chronic-fatigue-syndrome/).

Interviewed live by Rene Montagne, when asked why people thought sufferers don't really have a disease, Dr Daniel Peterson, medical director of the WPI, was clear: "*I think the reason for that is the abnormalities of the immune system are initially very subtle. And if a physician does just routine testing – you find they're normal. It isn't until you look at the immune system that you realise there's substantial dysregulation…It's very similar to asymptomatic carriers of HIV. They look just fine until time passes and their illness evolves and more symptoms are found. **But I never felt this was predominantly a psychiatric disease or malingering. There was never any evidence to support that theory…**Once it was demonstrated that the patients had impairment of the natural killer cells function, regardless of what country they were in, we knew that there was immune impairment…Back in the 1990s, I was associated with Temple University and researchers (who) looked at the antiviral pathway…found very substantial abnormalities in the patients who had chronic fatigue syndrome. And the illness is totally compatible with a viral illness that just doesn't go away"* (http://www.npr.org/templates/story/story.php?storyId=113650222).

Following the (re)discovery of a direct link between a retrovirus and ME/CFS, there has been much internet traffic about the dismissing and ignoring by US agencies of state of Dr De Freitas et al's work two decades ago that demonstrated a potential retroviral link, particularly in relation to possible transmission via blood products.

This down-playing has been ascribed by some people to (i) a possible UK/US collaboration over the use of biowarfare agents, including borrelia ("US Government Admits Lyme Disease Is A Bioweapon": http://www.indymedia.org.uk/en/2005/11/328067.html), (ii) the CDC's apparent determination to prevent at any cost public panic over the emergence of another AIDS-like pandemic and (iii) the wish to protect insurers from having to make payments for another chronic disease, factors that may be instrumental in Dr Bill Reeves' dismissive comments about the latest discovery of an association between a retrovirus and ME/CFS:

- the journal Nature reported: "*William Reeves, principal investigator for the Centres for Disease Control and Prevention (CDC)'s CFS public health research programme, says the findings are **'unexpected and surprising'** and that it is **'almost unheard of to find an association of this magnitude between an infectious agent and a well-defined chronic disease, much less an illness like CFS…Until the work***

is independently verified the report represents a single pilot study'. *He also notes that CFS…likely arises from a combination of many factors"*

- the Los Angeles Times also reported Reeves' comments, adding his comment that: ***"****It is extremely difficult to prove causation with a ubiquitous virus like XMRV, and it* ***'is even more difficult in the case of CFS, which represents a clinically and epidemiologically complex illness'*** *he said. Unfortunately, Reeves said,* ***the major flaw of the study is that there is not enough information about how subjects were selected to rule out any bias in choosing them"***

- the New York Times (13th October 2009) reported Reeves as saying ***"he was surprised that a prestigious journal like Science had published it****….We and others are looking at our own specimens and trying to confirm it…****If we validate it, great. My expectation is that we will not****'….Many patients and a community of doctors and researchers who specialise in the syndrome take issue with the (CDC's) approach to the illness and the way it defines who is affected. They claim that the CDC includes people whose problems are purely psychiatric, muddying the water and confounding efforts to find a physical cause"* (it is the case that the CDC now uses Reeves' own (2005) definition that does not distinguish between CFS and major depressive disorder, so it is to be anticipated that the CDC will not replicate the Mikovits et al findings).

Against this background, there are mounting calls for the removal of Dr Reeves from his position as principal investigator of the CDC's CFS research programme ("Support the 500 Professionals of the IACFS/ME – Reeves Must Go"):

"*On May 27th and May 28th, 2009, the Chronic Fatigue Syndrome Advisory Committee (CFSAC) convened in Washington, D.C. Among their recommendations to the Secretary of Health and Human Services was a call for new and progressive leadership at the CDC's ME/CFS research division. Under Bill Reeves' regime, funding has routinely decreased and increasingly broad definitions which have ceased to have any clinical meaning or research value have been implemented…. Under Reeves' direction the CFS program is being slowly strangled….* ***What does Reeves say about Mikovits' recent discovery? Without doing any study or due diligence, Reeves dismisses the findings****… Inaccurate stereotypes persist because Bill Reeves has not been accurately educating the public on the seriousness of this disease"* (Co-Cure ACT: 25th October 2009).

Comments such as that by Tom Kindlon from the Irish ME/CFS Association reflect the position of many in the international ME/CFS community: "***What does he mean 'much less an illness like CFS'****? CFS is much more like a chronic viral disease than most chronic diseases.* ***Why is he heading a programme based in the viral section of the CDC if he has this attitude?****"* (Co-Cure ACT:8th October 2009).

In her customary robust manner, Hillary Johnson in the US is scathing about Bill Reeves: ***"There isn't anything Reeves said to the press that was scientifically correct, one of the scientists associated with this work told me recently****…****How about Bill's comment, expressed to the New York Times, that he was 'surprised' a 'prestigious journal like Science' had published the study…Frank Ruscetti isolated the first human retrovirus infection HTLV (Human T-cell Leukaemia / Lymphoma Virus) at the National Cancer Institute 30 years ago. Bill thinks Ruscetti doesn't know what he's doing? Bob Silverman was a co-discoverer of XMRV; Silverman doesn't know what he's doing? Science was duped?*** *Is he kidding? Bill also suggested the paper didn't mean much because he, Bill, didn't know how the patients were selected. The patients were clinically defined by every medical criteria, including the CDC's. What more does Bill want? By now, most will have heard about Bill's comment that XMRV is a ubiquitous virus. That must have been a whoo-hoo moment for the Science collaborators. These collaborators didn't just arrive on the scene last month…they knew going into this work what the CDC did to Elaine De Freitas and her retrovirus finding in 1991. They understood the politics. They were aware of the agency's multi-million dollar propaganda war on a million very sick people. They were prepared. They CDC-proofed this study. The rigour in the Mikovits-Ruscetti-Silverman paper was such that Science had to take the paper"* (Co-Cure NOT: 25th October 2009).

Notably, Dr Stuart Le Grice, head of the Centre of Excellence in HIV/AIDS and cancer virology at the National Cancer Institute went on record saying: *"NCI is responding like it did in the early days of HIV"* (in other words, by dismissal and denial of the significance). As Cort Johnson observed: *"Neither the CDC nor the NIH (with the exception of NK cells) have shown any interest in pathogens of the immune system in over ten years. Research into ME/CFS has declined precipitously in both institutions over the past five years"* (http://aboutmecfs.org/blog/?p=920).

In response to an article in Nature by Lizzie Buchen who quoted Judy Mikovits as saying: *"I can't wait to be able to tell my patients…It's going to knock their socks off. They've had such a stigma. People have just assumed they were just complainers who didn't handle stress well"*, a comment posted on Nature News by John Smith captures the reality: *"The nature of this seriously disabling disease has taken so long to establish because of the paucity of serious biomedical research into the condition and the failure of government to support such research.* ***As a scientist who has suffered from it for over 25 years following viral infection I have watched, appalled, as scientific politics have deflected funding away from biomedical studies towards psychosocial ones. This is nothing short of a scientific scandal"*** (http://www.nature.com/news/2009/091008/full/news.2009.983.html).

In the UK, Simon Wessely is similarly unpopular, and for similarly well-founded reasons. On 5th February 1999 the New Statesman carried an article by Ziauddin Sardar about Wessely (Ill-defined notions) in which Sardar wrote:

"Once upon a time, if you were sick, you were really sick. You had a collection of recognisable symptoms. Now if you are ill there may not be a 'cause'. You may be suffering from something but you may not be ill at all — according to the medical establishment anyway (because) the 'cause' of some illnesses is better seen as a lifestyle than a pathogen.

"Sickness is no longer simply a personal matter; it has become social, political, bureaurocratic….When is someone sick, really sick? Who decides? By what criteria and procedures?…The only thing that is certain is that the patient himself / herself has little power and cannot answer any of these questions. You are ill only when someone says you are ill.

"Consider syndromes. Once this was a name for a collection of symptoms for which no clear cause had yet been found. Now it stands for a bunch or bunches of symptoms lacking even the security of certainty that they are actually there…Most notorious is "chronic fatigue syndrome". At the far extreme, it is known as "ME"…From its first recognition as a large-scale problem....horror stories abound of people (some of them children) whom the medical and psychiatric experts considered to be just faking...

"The same can be said of Gulf War syndrome.…again, there are lots of nasty symptoms: mild to moderate chronic fatigue, double vision, severe urinary and sexual problems, memory loss, joint and muscular pain — to start with…But even though 400 veterans have actually died and some 5,000 are suffering from illnesses related to Gulf War syndrome, the syndrome does not officially exist.

"All the actors involved in this drama have their own perspective.…the government with avoiding paying compensation at all costs. So one would expect the Ministry of Defence to deny the existence of Gulf Way syndrome and it does, operating on the simple basis of "no bug, no dosh".

"...this makes life very hard for sufferers. They not only have to survive their disease: they must also fight for elementary decency. And that is a long and bitter task in itself.

"But what of researchers? Why should they deny the existence of Gulf War syndrome? The struggle over recognition hinges on research. But this research is a totally different exercise...How do you investigate this mess of symptoms? Not with biochemistry, but with psychiatry.

"The new societal syndrome of syndromatic diseases requires a new speciality, a syndromologist. Fortunately, one is to hand. His name is Professor Simon Wessely, consultant psychiatrist at the School of Medicine, King's College, London.

"Wessely has been arguing that ME is a largely self-induced ailment that can be cured by the exercise programme on offer at his clinic.

"Recently he published the results of "the most definitive study" of Gulf War syndrome in.. .the Lancet... .It concluded — surprise, surprise — that there is no such thing as Gulf Way syndrome.

"So Wessely, who occupies a key position in our socio-medical order, denies the existence of Gulf War syndrome, just as he denies the existence of ME.

"Clearly, he is a follower of Groucho Marx: 'Whatever it is, I deny it'. Not surprisingly, lots of people hate him.

"If Simon Wessely is our syndromologist-in-chief, who has chosen and vetted him for that post, and by what criteria and procedures? Where is the debate over the shaping of such research?…When will we have the first officially sponsored study of such a problem which the sufferers do not have the occasion to call a whitewash?".

Since at least 1994, when the CFIDS Chronicle published an article titled "The Views of Dr Simon Wessely on ME: Scientific Misconduct in the Selection and Presentation of Available Evidence?" (Spring 1994:14-18) valid criticisms of Wessely have continued to mount, some of which can be accessed on http://www.meactionuk.org.uk .

In his article in New Scientist on 9th October 2009 (referred to above), Ewen Callaway noted Professor Wessely's position regarding the discovery of XMRV in CFS patients: "*Wessely points out that XMRV fails to account for the wide variety of other factors associated with the CFS, including childhood trauma…'Any model that is going to be satisfactory has to explain everything, not just little bits' he says".* Wessely's belief that childhood trauma causes ME/CFS takes no account of those who had a happy, secure childhood within a stable and loving family but who still developed severe ME/CFS.

Similar points are reflected in the many online comments posted to the New Scientist. These were highly critical of Wessely's dismissive attitude, and provided examples of the adverse impact on patients of his ill-grounded beliefs about ME/CFS, for example:

"Dr Wessely had the chance to prove he had some kind of humility with regard to his disgraceful behaviour towards 'CFS' "

"Now if that's not the sound of a desperate drowning man clinging to the sinking wreckage of his fatally flawed theory for ME. Give it up, Wessely, sink to the bottom of the sea, vanish without trace. The time has come once and for all to banish these primitive psychological theories to the dustbin of medical history, where they so rightfully belong"

"Completely agreed – Simon Wessely, the medical establishment and local authorities that have taken children into care, sectioned adults, forced harmful treatment, ruined lives, should be made to apologise to every single one of their victims, not only here but worldwide"

"Holding a different evidence-based view-point is one thing – ignoring evidence and letting ego condemn patients to grotesque suffering and death as a physician is evil and should be dealt with as such"

"I look forward to seeing the psychological research by Professor Wessely published in the journal Science"

"I was diagnosed with ME in 1992–3…I'm a former clinical specialist in life-support technology, qualified in medicine, perfusion science and life-support technology, so I know a bit about all this. I empathise with anyone who has genuinely suffered this condition, especially when they have not had good treatment from their own doctors"

"To the Editor: It remains a mystery as to why you bother including the unsubstantiated opinion provided by Dr Simon Wessely. He continues to profit from the prescription of cognitive therapy for this serious illness, despite the fact

that the majority of patients fail to benefit from such interventions. By any other model, insistence upon cognitive therapy as the default model for treatment should constitute malpractice"

"I saw on my doctor's notes that the symptoms were all in my 'mind'. This was despite a low white cell count, inflamed spleen and swollen lymph nodes. Yep, the low white cell count was because of my 'mind'. If they dismissed cancer this way the overpaid morons would be sued for malpractice;

"Those physicians may have some red-faced explaining to do if this research pans out"

" 'Red-faced' – no, they should be sued for negligence. Sorry, but I was damn near killed by such idiocy so I have not the slightest sympathy for such bigoted physicians…I want several prominent persons responsible for this terrible abuse of millions of ill people across the globe criminally charged and tried for negligence…Many people have DIED because of this, either by direct abuse by doctors, or by disdainful refusal to aid, or actively preventing research into physical causes. Sophia Mirza is only one such victim, most others just sank without trace as it was 'inconvenient' and their death or suicides were 'all their own fault as it was all in their heads'. But when a physician deliberately ignores his duties because of prejudice – that, sir, is ABUSE. Imagine how an MS sufferer would feel if they were ignored, abused, even sectioned by the very physician who swore an oath to help them. And then the very person at the top of the pyramid of abuse was allowed to publish articles about MS…"

"But, Simon, you said they thought themselves sick…Wessely points out that XMRV fails to account for the wide variety of other factors associated with the CFS, including childhood trauma….but Professor Wessely was quite happy to lead nations to think that these unfortunate people were all suffering from 'abnormal illness beliefs'. Why was he so happy to ignore biomedical research which demonstrated that this disease was not a mental illness?"

"Simon Wessely…(has) a lot to answer for…I have yet to meet someone with ME who hasn't inspired me with their strength. It's just a shame there is so much to fight against"

"The idea that ME was somehow linked to childhood trauma was always nonsense…Way back when I was first ill, researchers were looking for a retrovirus. The problem was that no-one would fund them and allow then to continue their work. They were repeatedly turned down and their work blocked. This retrovirus should have been discovered at the same time as AIDS and the last few miserable decades of my life could have been avoided…No more excuses and no more psychobabble"

"Tragically for sufferers, the psychological zealots are ruling the asylum and they have steered successive definitions away from viral, inflammatory disease and to their beloved 'unexplained fatigue' and disingenuous 'psychological factors'. Mediocre findings of CBT/GET have been spun more than a New Labour carousel leading a character assassination on the ME community, creating an ideological distortion of the very presentation of the disease, whereby misled doctors dismiss such unfortunate patients as 'pond life' or 'ME lunatics' and deny even the most severely affected (eg bedbound) patients access to investigation, treatments, monitoring, advocacy and education of social and welfare support networks, while taking no interest in/dismissing the literature themselves. Cue great neglect, suffering, exploitation, wasted generations and premature deaths. Will the psych/med profession apologise? Just as with past outrages against multiple sclerosis (and) Parkinsons, will they hell" (http://www.newscientist.com/commenting/browse;jsessionid=5E5EAC8B3582B288ADB3A7F9F2D0611A?id=dn17947).

Other similar comments about Wessely were posted in response to The Independent's coverage of the XMRV discovery, for example:

*"**This is the time for Simon Wessely to walk away and shut the door. We don't want to see him ever again mentioned in relation to this disease. Didn't he read the news – 500 blood samples form London are being tested and the figures are holding up**…I have spent my entire adult life with this disease and I would like to have some illness-free years before I die. **The UK government and medical research council squandered millions chasing a psychological cause"***

"I know as bad as things are in the U.S. in regard to ME, the UK seems even worse. That Wessely guy is a total moron. This disease has so many consistent biological abnormalities across the ME/CFS population and they are continually being ignored. Will these people ever listen?"

***"Wessely, it is time for you to accept the truth and give up**. I have had ME for 7 years and it has completely consumed my life. **Money put into the research has been very limited, mostly due to the political connections of Wessely, his partner and the labour party. I know. I worked in there**"* (Wessely's wife was / is a senior policy advisor to the Department of Health; she is Vice Chair of Council of The Royal College of General Practitioners and is Chair of the RCGP Medical Ethics Committee)

"*It's in Simon's mind: I have lost 15 years to CFS and exhortations that CBT and graded exercise (which I have done in spades) have on more than one occasion pushed me to the edge…What a pathetic scam to let millions suffer on a pretence"*

"I wholeheartedly agree with comments made against Simon Wessely. His title says it all – professor of psychological medicine. ***Unfortunately there are a great many people like him who have held back the frontiers of modern research by dismissing the findings and instead promoting psychological causes"***

"Mr Wessely's views. Time to put your cards on the table. I find it interesting that Wessely is so keen to keep ME 'all in the mind', especially with a growing mass of evidence to suggest otherwise. I'd like to see his funding resources revealed…I'm sure that behind closed doors there is more going on to douse the flame of truth than we actually know about"

"I was very saddened to read Simon Wessely's comments…and personally feel that the psychological explanation for ME/CFS is far from satisfactory"

"I worked in the Civil Service for both Jacqui Smith and Alan Johnson (the former was Home Secretary and the latter was Secretary of State for Health). *Once I became disabled with CFS I was horribly bullied by the Civil Service. It was a truly terrible time, trying to cope with a life-altering disability and an employer who did not care".*

On other sites (for example; http://www.meactionuk.org.uk/wessely.html), people recalled what Wessely has said and published about ME/CFS in the past, for example:

"What lies behind all this talk of viruses and immunity?…..Talk of viruses and the immune system is now embedded in popular consciousness….Viruses are an attribution free from blame…there's no blame, no shame and no stigma….And (mocking) ***here is the virus research doctor himself to protect us from that shame….And what is it he delivers? Respect"*** (Microbes, Mental Illness, the Media and ME: The Construction of Disease. 9th Eliot Slater Memorial Lecture, Institute of Psychiatry, 12th May 1994).

"***Wessely sees viral attribution as somatisation par excellence"*** (Helen Cope, Anthony David, Anthony Mann. Journal of Psychosomatic Research 1994:38:2:89-98).

In her exposition of the role of the late Dr Stephen Straus of the NIH in what seems unquestionably the "cover-up" of ME/CFS by US agencies of state (PERP Walk: A Reality Crime: http://www.oslersweb.com/blog.htm?post=635977), Hillary Johnson supplies quotations of Straus' own words in which he provided thousands of doctors with the "official" US government line on "CFS" (ie. that people who developed CFS had a life-time history of psychiatric illness, a view that was sent to approximately 500 reporters and news organisations, including television networks and the science and government writers for every major newspaper and wire service). This was based on a study of just 28 participants, one of whom (psychoanalyst Susan Simon) talked of suing Straus for medical malpractice; in 1993 she was killed instantly when a truck collided with her motorised scooter on a New York city street.

One comment about Johnson's article on Straus may be pertinent:

"Just because one is blessed with a keen mind and is granted a position of importance, it very obviously does not preclude the psychopaths, the bigots, the narrow minded or just plain xenophobic from taking control of areas of public office that have great bearing upon everyone's lives. And then there is Straus – who fits the bill for all of the above – and of course he carried the child-like characteristic of being unable to accept that he was wrong…It is just a shame that people have to die for those with ME/CFS to get an answer. And by that I mean that people such as Straus should step out of the way when they have no answer. ***Wessely should. White should. Sharpe should****".*

In a reply to someone who wrote to him on 12th November 2009 asking for his response to the XMRV findings, Wessely replied: *"Could be a real breakthrough, even if I still don't understand how they made the leap from prostate cancer to CFS"*, which seems to indicate that Wessely remains ignorant of or else does not understand what Judy Mikovits et al said: "***both are linked to alterations in the antiviral enzyme RNase L"***, a link that was clearly explained by David Bell in his Lyndonville News, volume 6, number 2, October 2009: ***"XMRV was first linked to human disease by Robert Silverman PhD at the Cleveland Clinic in patients with prostate cancer who also had a defect in the RNase L antiviral pathway. As this pathway has been known to be abnormal in CFS, it was reasonable to search for the virus in CFS"***. Wessely then seemed to deny the association with XMRV and cancer: "*I am worried that 20% of the CFS patients seem to have lymphoma (ie cancer), which might be fascinating for our knowledge of cancer* ***but really isn't relevant for CFS****"*. Apparently adopting the same stance as Bill Reeves in the US, Wessely continued: *"I would be very surprised indeed if others find rates of XMRV at the same level as this paper"* (Co-Cure ACT: 12th November 2009).

There is international recognition that Wessely *"is employed by the Ministry of Defence and NATO (he chaired a committee on psychological responses to WMD – weapons of mass destruction) and heavily backed by corporate interests to deny the reality of chronic illnesses such as ME/CFS, Gulf War Illness, Lyme Disease, Multiple Chemical Sensitivity and others…****Wessely's name is known to the thousands of sufferers of chronic illnesses in Britain and abroad who have been hurt by his philosophy…For years Wessely has been the outspoken proponent of the view that chronic physical conditions such as Gulf War Illness, ME/CFS, fibromyalgia, Lyme Disease, MCS and others are simply 'all in the head' of the sufferer. This view has received great support from the Government and from the Army, both here and in America.*** *It has also been enthusiastically promoted by insurance companies and the Department for Work and Pensions.* ***Millions of public research funds have gone into the pockets of psychiatrists following the Wessely school of thought. The result: seriously ill patients have been denied recognition and treatment, disability benefits and dignity. They have been ridiculed by doctors and vilified in the press. Stigmatised by Wessely and his followers as malingerers, hypochondriacs, or simply 'mad', sufferers of chronic physical illnesses have been left untreated for years, sometimes ending up paralysed, amnesic or even dying****.* *Some commit suicide under the pressure of isolation and never-ending pain.* ***Providing no evidence base for his conclusions, Wessely nevertheless rides roughshod over published medical studies linking vaccine damage, chemical exposure etc with Gulf War Illness (and) toxic chemical exposure (and) viruses with fatiguing illnesses. He does not disprove the evidence of physical causes for these diseases – he just ignores it****"* (http://www.indymedia.org.uk/en/2006/01/331967.html).

As long ago as 1998, in his article "Dr Simon Wessely: Prophet or Profit?", Dr Ken Jolly, a GP in New Zealand who had to give up his medical practice because of ME/CFS, published his concern that Wessely et al had come to dominate thinking about ME/CFS even in New Zealand, saying that they had achieved such influence by producing vast volumes of papers on CFS and obtaining funding for their own work. Jolly was forthright:

"I feel it is time sufferers in NZ became aware of his growing influence. The existence of this influence is no new to UK sufferers and it has affected how they are being treated, as well as their accessibility to aid and financial assistance. Clinicians with opposing views are being sidelined by most of the prestigious medical journals. Why this is so is unclear. Simon Wessely is very politically astute (and) has been able to sway many to his way of thinking. He has also developed a 'patter' which he uses to convince patients of the rightness of his model. In reality, this is a smokescreen which effectively covers his true underlying beliefs. ***But 'the clincher' for convincing many medical scientists of any theory is to back it up with reliable research data. He and his colleagues have 'appeared' to do this, almost putting an end to the oppositional cries from the physical camp. However, these trials have been***

flawed in every way imaginable…Unfortunately people like Simon Wessely, in my opinion are not only using up large amounts of valuable research monies but are also diverting research along blind paths…*I will now attempt to summarise Simon Wessely's and colleagues' views about ME. The reason I have chosen to mainly discuss Simon Wessely rather than the others of the group is because it so often appears that he is the mouthpiece for their statements".*

Dr Jolly then lists some of the more notorious of Wessely's published views, including Wessely's belief that CFS is merely the extreme end of normal fatigue which, as Jolly points out, totally ignores the cyclic nature of the disorder that is a pattern commonly seen in autoimmune diseases. Jolly also points out that Wessely's claim that ME/CFS patients' symptoms are caused by hypervigilance towards normal bodily sensations does not explain why the same symptoms are reported by thousands of patients worldwide (who may not even speak the same language). Jolly notes that many physically-based research findings *"have frequently been ignored for the (Wessely) model to continue to fit".* Jolly is particularly scathing about Wessely's view that patients perpetuate their own illness: "*This is insulting to their intelligence. In my experience patients undergo enormous financial, social and relationship losses because of this illness. Additionally, they are prepared to go to almost any lengths to get better – NOT the actions of people perpetuating a condition associated with non-activity"* (http://www.indymedia.org.uk/en/2006/01/331967.html).

As Dr Jolly further noted: "*The effect that Simon Wessely may have in the future on how doctors view ME cannot be underestimated. His viewpoint seems to have pervaded the thinking of the medical establishment in the UK. The most worrying aspect is that these theories suit those who are politically in charge and many institutions and governments are already being seduced to this way of thinking…Why Simon Wessely has pursued this theory with such tenacity somewhat eludes me.* ***He has encountered massive opposition from many quarters****".*

An internet search will quickly reveal that there is extensive outrage about Simon Wessely and his colleagues' unproven beliefs, not only from ME/CFS patients and their long-suffering families, but also from international medical scientists and clinicians who are not blinded by ideology or vested interests.

In his article in The Independent on 9th October 2009 (referred to above), Steve Connor also quoted Professor Simon Wessely's views on the implications of the XMRV discovery: *"Other researchers emphasised that the numbers published so far are too small to conclude anything about the cause of chronic fatigue syndrome. 'It's spectacular but needs replicating. And I hope that no-one is thinking of prescribing anti-retrovirals on the basis of this, said Simon Wessely, professor of psychological medicine at King's College, London****. 'It's very preliminary and there is no evidence to say this is relevant to the vast majority of people in the UK with the condition'*** *".*

However, in a Leading Article that same day, The Independent said:

"…for many years doctors argued that Chronic Fatigue Syndrome didn't exist. They refused even to dignify it with the name Myalgic Encephalomyelitis. ME, they said, was just 'me' writ large… Scientists could be on the brink of a breakthrough. We must hope they are. That would – at least – go some way to compensating for the shameful manner in which sufferers were treated for so long by the medical profession".

On 29th October 2009 Professor Coffin told a Department of Health and Human Services Committee that this discovery was of ***"potentially extraordinary importance****",* not least, as Jack Johnson reported (Co-Cure NOT:16th November 2009), because it means validation and hope for millions of people suffering from (ME)CFS, often thought by many to be nothing more than the product of neurosis and even laziness and, as Jack Johnson pointed out: "***CFS has long been thought to be linked to retroviral infection****".*

As noted in "Denigration by Design? A Review, with References, of the Role of Dr (now Professor) Simon Wessely in the Perception of Myalgic Encephalomyelitis (Up-date) Volume II (http://www.25megroup.org/denigration%20by%20design/denigration%20contents.htm), it seems that to Wessely and his closest associates, the belief of the moment represents the only truth.

They would do well to remember that in the early 1600s, King James of England (who was also King James VI of Scotland) wrote a book called "Demonology" and that book helped to send to their death women known as the Lancashire witches. Countless innocent women were persecuted, tortured and executed as witches, having been forced into admitting things they did not do, the majority being people who suffered from mental illness.

Incredibly, it was not until the 1950s that the Witchcraft Act was repealed in the UK. This must surely serve as a salutary reminder that the belief of the time (currently, that ME/CFS is a behavioural disorder) is not necessarily the truth, even though it might be promoted as the truth.

It is fair to say that the views of Wessely and his close colleagues (including those involved with the PACE Trial) are held in contempt by many people – medical and lay alike – who have to deal with the reality and severity of ME/CFS; yet injustice for those with ME/CFS continues. Cases of untold suffering and despair continue to accumulate, and this is very significantly because of the influence of the Wessely School.

One can but pray that along with his colleagues Peter White, Michael Sharpe and Trudie Chalder, Wessely's power and influence – unlike that of demonology – will not remain enshrined for the next 350 years and that medical science may at last have provided the means to right the wrongs that the Wessely School have done so much to perpetrate upon those with ME/CFS.

That such wrongs exist in the US also is exemplified by the testimony of Kenneth Friedman on 30th October 2009 before the CFS Advisory Committee (Co-Cure NOT:MED: 4th November 2009). Friedman, a medical school professor at the Department of Pharmacology and Physiology, New Jersey Medical School, said:

"*I have been asked to comment upon the status of Chronic Fatigue Syndrome education in the United States.*

"The Director of the Office of Ethics and Compliance has informed me that my off-campus activities relating to CFS which include testifying before this Committee, serving on this Committee, providing continuing medical education courses, establishing medical student scholarships and assisting with healthcare legislation are not part of my responsibilities as a University Professor.

" I am told that I will be punished with a penalty as severe as termination of my employment for these activities.

"I am not a unique target. Colleague Ben Natelson (an ME/CFS researcher who was Professor in the Department of Neurosciences at New Jersey Medical School) *has left the same school.*

"A different medical school has refused to permit access to their medical students to discuss CFS.

"A statewide healthcare provider…refuses to permit a CFS training session for their physicians.

"The failure of the CDC to convince the medical-academic establishment of the legitimacy of CFS, and the urgent need for its treatment, has created this environment".

Could it be said that the Wessely School has created a similar environment in the UK and that the MRC PACE Trial is part of that constructed environment, just as the NICE Clinical Guideline and the actions of NICE which resulted in the failure of the Judicial Review were also part of it?

It is certainly the case that, to the great detriment of patients with ME/CFS, clinicians experienced in ME have been prevented from working in the "CFS" clinics that are often run by non-medical staff such as occupational therapists.

As Professor Leonard Jason pointed out on 30th May 2008 (New York Times Essentials):

"With cancer or AIDS, you have an immediate feeling from your family, your work associates, your friends, that (these are) something we need to make accommodations for. What's strikingly different about this illness is that the majority of people not only have to deal with a particularly debilitating health problem, they also have to deal with the stigma and societal reaction and disbelief and illegitimacy, and that is crushing.

"If (the case definition) includes people who don't have the illness…one needs to be wary of that, because …if you have patient samples that are different, ultimately what will happen is it's very hard to find genetic or biological markers because there's such imprecision in how it's been identified. So what happens is that people will say 'We can't find anything, it must be psychogenic'.

"The epidemiology done by the CDC was atrocious…it had a case definition that was put together by consensus and not by research methods (referring to the 1988 Holmes et al definition) *and it had a name that was pretty trivialising. The prevalence research was very poorly done. The tests they were using were inappropriate and had a real bias for psychiatric morbidity".*

It could be said that, due to the influence of the Wessely School, exactly the same situation exists in the UK two decades later.

There are many more such papers; the above are merely illustrative of the significant evidence-base consisting of thousands of papers which demonstrate that ME/CFS is not a behavioural disorder as asserted by the Wessely School.

Objective signs in ME/CFS

From the above illustrations, it will be readily understood that, despite the Wessely School's insistence that there are no objective signs of organic disorder in ME/CFS, there are numerous objective reproducible abnormal signs that are discernable by any reasonably competent physician. They include the following:

- labile blood pressure (this is a cardinal sign); low systolic BP -- <100 in 50%
- nystagmus and vestibular disturbance (vestibular dysfunction seen in 90%)
- sluggish visual accommodation
- fasciculation
- hand tremor
- neuromuscular incoordination
- cogwheel movement of the leg on testing
- muscular weakness
- marked facial pallor
- postural orthostatic tachycardia syndrome (POTS)
- positive Romberg
- abnormal tandem or augmented tandem stance
- abnormal gait
- evidence of Raynaud's syndrome and vasculitis (vascular signs cross dermatomes)
- mouth ulcers
- hair loss
- singular reduction in lung function (shortened breath-holding capacity seen in 60%)
- enlarged liver (not usually looked for by psychiatrists)

The problem is that many doctors refuse to examine ME/CFS patients – or even to lay a finger on them – because ME/CFS patients are largely despised by the medical profession. Indeed, in 1994 one of the medical trade magazines published an article entitled "GPs despise the ME generation" (GP: April 1994). The article

itself said at the time: *"studies have shown that that most ME patients rate contact with medical services as unhelpful"* and little has changed in the intervening fifteen years.

Abnormal findings on testing include flattened or even inverted T-waves on 24 hour Holter monitoring; abnormal glucose tolerance curves; elevated lactate levels in the ventricular system (seen in 70% of patients); neuronal destruction and elevated choline peaks (seen in 10% of patients); punctate lesions consistent with small strokes (seen in 78% of patients); very poor oxygen transport on pulse oximetry readings (seen in 90% of patients) and an abnormal venous blood gas picture.

None of these can rationally be explained as evidence of a behavioural disorder.

Symptoms and signs regularly noted in ME/CFS include:

extreme malaise; abdominal pain and diarrhoea; post-exertional exhaustion almost to the point of collapse; inability to stand unsupported for more than a few moments – this is a classic finding in ME/CFS; sometimes too weak to walk (different from deconditioning); inability to walk upstairs or to maintain sustained muscle strength, as in repeated brushing of hair with arms elevated, or inability to carry a shopping bag, or dry oneself after a bath, peel vegetables or prepare a meal; neuromuscular incoordination, not only of fine finger movement with clumsiness and inability to control a pen and to write legibly, but also of the larynx and oesophagus -- a frequent complaint is the need to swallow carefully to avoid choking; oesophageal spasm and pain; dysequilibrium ie. loss of balance; staggering gait (ataxia); bouts of dizziness and frank vertigo; difficulty with voice production, especially if speaking is sustained; aphasia (inability to find the right word); muscle cramps, spasms and twitching; black-outs and seizure-like episodes; spasmodic trembling of arms, legs and hands; episodes of angor animi (brought about by abrupt vasomotor changes that cause the sufferer to have uncontrollable shaking, like a rigor, and to think they are at the point of death) – it is essential to understand the terror that such attacks induce in a patient, and no patient can fake them; photophobia; difficulty focusing and in visual accommodation, with rapid changes in visual acuity; blurred and double vision, with loss of peripheral vision; eye pain; swollen and painful eyelids, with inability to keep eyelids open; tinnitus; hyperacusis, for example the noise of a lawnmower can cause acute distress and nausea; heightened sensory perception (for example, acute sensitivity to being patted on the back; inability to tolerate lights, echoes, smells, movement, noise and confusion such as found in a shopping mall or supermarket without being reduced to near-collapse); frequency of micturition, including nocturia; peripheral neuropathy; numbness in face; altered sleep patterns, with hypersomnia (in the early stages) and insomnia (in the later stages); alternate sweats and shivers; temperature dysregulation, with intolerance of heat and cold; parasthesias; sleep paralysis; intermittent palindromic nerve pains; tightness of the chest alternating with moist chest; muscle tenderness and myalgia, sometimes burning or vice-like; typically shoulder and pelvic girdle pain, with neck pain and sometimes an inability to hold the head up; orthostatic tachycardia; orthostatic hypotension, and symptoms of hypovolaemia, with blood pooling in the legs and feeling faint due to insufficient blood supply to the brain; labile blood pressure; intermittent chest pain akin to myocardial infarct; segmental chest wall pain; subcostal pain; vasculitic spasms, including headaches; cold and discoloured extremities, with secondary Raynaud's; easy bruising; peri-articular bleeds, especially in the fingers; shortness of breath on minimal exertion; the need to sleep upright because of weakness of the intercostal muscles; pancreatic exocrine dysfunction leading to malabsorption; rashes (sometimes vasculitic in nature); flushing of one side of the face; ovarian-uterine dysfunction; prostatitis; hair loss, and mouth ulcers that make speaking and eating difficult. The notable point about symptoms in ME/CFS is their variability.

All the above symptoms and more are documented in the literature; they bear little resemblance to "chronic fatigue" or to a "continuum of on-going tiredness", a description of "CFS/ME" often used by the Wessely School.

In summary, the MRC PACE Trial Principal Investigators ignore the published evidence (not hypotheses) of the following that have been documented in ME/CFS:

- evidence of disrupted biology at cell membrane level
- evidence of abnormal brain metabolism
- evidence of a reduction in grey matter
- evidence of widespread abnormal cerebral perfusion (hypoperfusion)
- evidence of central nervous system / immune dysfunction
- evidence of central nervous system inflammation and demyelination
- evidence of hypomyelination
- evidence of spatial disorientation
- evidence that ME/CFS is a complex, serious multi-system autoimmune disorder (in Belgium, the disorder has now been placed between MS and lupus)
- evidence of significant neutrophil apoptosis
- evidence that the immune system is chronically activated (eg. the CD4:CD8 ratio may be grossly elevated, as seen in multiple hypersensitivities)
- evidence that NK cell activity is impaired (ie. diminished)
- evidence of hair loss in ME/CFS
- evidence that the vascular biology is abnormal, with disrupted endothelial function
- novel evidence of significantly elevated levels of isoprostanes (a marker for oxidative stress, which in ME/CFS goes up with exercise intolerance)
- evidence of impaired proton removal from muscle during exercise
- **evidence of cardiac insufficiency and that patients are in a form of heart failure**
- evidence of autonomic dysfunction (especially thermo-dysregulation; frequency of micturition with nocturia; haemodynamic instability with labile blood pressure; pooling of blood in the lower limbs; reduced blood volume (with orthostatic tachycardia and orthostatic hypotension)
- evidence of respiratory dysfunction, with reduced lung function in all parameters tested
- evidence of neuroendocrine dysfunction (notably HPA axis dysfunction)
- **evidence of recovery rates for oxygen saturation that are 60% lower than those in normal controls**
- evidence that the average maximal oxygen uptake was only 15.2 ml/kg/min, whilst for controls it was 66.6 ml/kg/min
- **conclusive evidence of delayed recovery of muscles after exercise**, with ME/CFS patients reaching exhaustion more rapidly than controls, with this failure to recover being more pronounced 24 hours <u>after</u> exercise (note: there is no evidence of de-conditioning)
- evidence of mitochondrial metabolic dysfunction
- evidence of inability to sustain muscle power
- evidence of greatly increased REE (resting energy expenditure)
- evidence of enteroviral particles in muscle biopsies
- **evidence of a sensitive marker of muscle inflammation (inflamed tissues should not be exercised)**
- evidence of on-going infection
- evidence that the size of the adrenal glands is reduced by up to 50% (with reduced cortisol levels)
- evidence that up to 92% of ME/CFS patients also have irritable bowel syndrome (80% of the immune system is located in the gut)
- evidence of abnormal gene expression (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**
- evidence of profound cognitive impairment (worse than occurs in AIDS dementia)
- evidence of adverse reactions to medicinal drugs, especially those acting on the central nervous system, such as anaesthetics
- evidence that symptoms fluctuate from day to day and even from hour to hour
- there is no evidence that ME/CFS is a psychiatric or behavioural disorder.

Dr Elizabeth Dowsett, a former President of the ME Association, was clear: "*There is ample evidence that ME is primarily a neurological illness, although non-neurological complications affecting the liver, cardiac and skeletal*

muscle, endocrine and lymphoid tissues are also recognised. ***The commonest causes of relapse are physical or mental over-exertion. The prescription of increasing exercise can only be counter-productive. Some 20% have progressive and frequently undiagnosed degeneration of cardiac muscle which has led, in several cases, to sudden death following exercise****. Neurological problems include* ***exhaustion, weakness and collapse following mental or physical exertion beyond the patient's capacity.*** *This arises from metabolic damage.* ***Problems with balance are common in ME due to involvement of spinal nerve tracts in the damaged brain stem****. Over 70% of ME patients suffer from significant bone and muscle pain (a further consequence of brain stem damage which seriously affects their mobility). Other patients have in addition metabolic damage to muscle fibres. 30% of patients with abnormal exercise tests have evidence of persistent infection in the muscles, and evidence of muscle infarcts. (Patients with ME exhibit) jitter due to incoordinated muscle fibre action, following damage to the neuromuscular junction. Patients with ME suffer a variety of symptoms arising from autonomic nervous system dysfunction, including liability to a dangerous drop in blood pressure on standing for more than a few minutes"* (http://web.archive.org/web/20080316210245/http://www.25megroup.org/Information/Medical/dowsett's/mobility+problems.htm).

In November 2006, the US Centre for Disease Control (CDC) announced its "CFS Toolkit" to inform not just the US but the whole world about the nature and severity of ME/CFS. The following are extracts from the Press Conference:

Dr Julie Gerberding, Director of the US CDC: *"One of the things that CDC hopes to do is to help patients know that they have an illness that requires medical attention, but also to help clinicians be able to understand, diagnose and help people with the illness.* ***But more importantly, to be able to validate and understand the incredible suffering that many patients and their families experience in this context****. We are committed to improving the awareness that this is a real illness and that people need real medical care and they deserve the best possible help that we can provide. The science has progressed (which has) helped us define the magnitude and understand better the clinical manifestations (and this has) led to a sorely needed foundation for the recognition of the underlying biological aspects of the illness. We need to respect and make that science more visible. I have heard from hundreds and hundreds of people who are telling their stories – their courage, their commitment to try to live the best possible life they can (and) the tremendous impact that this is having on their ability to function".*

Dr William Reeves, Chief of Chronic Viral Diseases Branch at CDC: ***"We've documented, as have others, that the level of impairment in people who suffer from (ME)CFS is comparable to multiple sclerosis, AIDS, end-stage renal failure, chronic obstructive pulmonary disease.*** *The disability is equivalent to that of some well-known, very severe medical conditions. We found that (ME)CFS follows a pattern of remitting and relapsing symptoms, the symptoms can change over time, and that spontaneous recovery is rare.* ***We found that the best predictor for (ME)CFS was intensity of the initial infectious disease****. The sicker the patient when s/he first got infected, the more likely they were to have persisting chronic symptoms.* ***There were no other factors, psychological or biological, that held up under thorough analysis".***

Professor Anthony Komaroff of the Harvard Medical School: *"****There are now over 4,000 published studies that show underlying biological abnormalities in patients with this 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.*** *A whole bunch of studies show that the hormone system is different in patients with (ME)CFS than in healthy people, people with depression and other diseases****. Brain imaging studies have shown inflammation, reduced blood flow and impaired cellular function in different locations of the brain. Many studies have found that the immune system appears to be in a state of chronic activation (and) genes that control the activation of the immune system are abnormally expressed in patients with this illness.*** *A number of studies have shown that there probably are abnormalities of energy metabolism in patients with this illness".*

Professor Nancy Klimas, Professor of Medicine, University of Miami: *"I've treated over 2,000 (ME)CFS patients. 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. ***There are diagnostic criteria that enable clinicians to diagnose (ME)CFS in the primary care setting".***

The full Press Conference is available at: http://web.archive.org/web/20080505120858/http://www.cdc.gov/od/oc/media/transcripts/t061103.htm?id=36410
Despite repeated international calls for biomedical research and for appropriate investigations of patients with ME/CFS, including more accurate subgrouping of those with "CFS", influenced by the Wessely School, the Medical Research Council maintains its psychiatric bias. From its own website, it is clear that approximately 91% of the MRC's total grant-spend on ME/CFS in the five years from May 2003 has gone on psychiatric trials of behavioural interventions carried out by the Wessely School themselves. Furthermore, the MRC is known to have turned down no less than 33 biomedical and pathophysiological research projects on ME/CFS.

Wessely School psychiatrists have continued to publish studies on "CFS", the results of which do not accord with existing biomedical science, for example: *"It has been argued that* ***perceived*** *functional incapacity might be a primary characteristic of CFS. (Our) sample consisted of 73 patients with a diagnosis of CFS according to the Oxford criteria randomly selected from clinics in the Departments of Immunology and Psychiatry at St Bartholomew's Hospital, London. The findings suggest that* ***perceived*** *functional incapacity is a primary characteristic of CFS"* (Priebe S et al. Psychopathology 2008:41(6):339-345).

To refer to "*perceived incapacity*" in these patients is not only offensive to patients but is also an insult to the many clinicians and researchers who have uncovered the reality of the incapacity through the scientific process (in which psychiatry plays no part).

The assumption by the Wessely School that CFS/ME is a "faulty belief system" that can be "corrected" by CBT and incremental aerobic exercise is fallacious. **The reality is that more than one UK Coroner (and many more internationally) has accepted ME/CFS as a cause of death, and the diagnosis appears on death certificates.**

No-one who is aware of this wealth of information can credibly doubt the reality, the validity and the devastation of this organic multi-system disease.

Documented International Concerns about CBT/GET for patients with ME/CFS

No consideration seems to have been given by the PACE Trial Principal Investigators --- nor indeed by the West Midlands Multi-centre Research Ethics Committee --- to the documented international concerns about CBT/GET for ME/CFS patients, for example:

United States:

"*Our reluctance to endorse graded activity arises from our vastly different clinical experience in the US"* (Friedberg F, Jason LA. American Psychological Association, Washington, 1998).

"Our clinical experience suggests that graded exercise / CBT for clients who do not exhibit fear-based avoidance may be counter-productive and trigger symptom flare-ups" (Fred Friedberg, Leonard A Jason, J Clin Psychol 2001:67:433-455).

Four US experts in ME/CFS are on record about the British approach to CBT:

"One of the most controversial treatments for ME/CFS is cognitive behavioural therapy. Some patients are fiercely opposed to it because they believe it suggests that if they'd just change their behaviour or their attitudes about the illness, they would get better. This opposition has been strengthened by the British approach to CBT".

" 'I don't take the British point of view that CBT is the one thing you can do to effectively treat ME/CFS' says (Professor) Klimas.

"Dr Lapp agrees. 'In my opinion CBT is widely but unfairly maligned because of the British approach, which presumes that ME/CFS has no organic basis and is therefore contradictory to current science. ***This type of CBT assumes somatic symptoms are perpetuated by errant illness beliefs and maladaptive coping'****.*

" Dr Bell (says) 'It won't suddenly make patients better'.

"Dr Peterson says he's 'not convinced of the efficacy of CBT' " (CFICS Chronicle Special Issue: The Science & Research of CFS: 2005-2006: 52-53).

Australia:

"*Many (CBT/GET) studies have significant refusal and drop-out rates, which may reflect on the acceptability of the treatment regimens"* (Royal Australasian College of Physicians Australian National Guidelines, M J Aust 2002:65:176 (8 Suppl):S17-S55).

Canada:

"*Exercise programmes must be entered into cautiously as clinical studies have indicated that symptoms worsened in approximately half of the ME/CFS patients"* (Canadian Guidelines on ME/CFS, produced by Health Canada Expert Medical Consensus Panel; JCFS 2003:11(1):7-115).

New Zealand:

"*GET may cause relapses and is therefore potentially harmful"* (New Zealand Guidelines Group: Report to the Ministry of Health, November 2003).

The UK Chief Medical Officer's Working Group Report

The UK Chief Medical Officer's Working Group Report of 2002 on "CFS/ME" recorded concerns about GET: "*Existing concerns include the view that patients have a primary disease process that is not responsive to or could progress with graded exercise.* ***Substantial concerns exist about the potential for harm****. No other treatment received such negative feedback"* (4.4.2.1:46-47).

Unremitting concern

This concern is un-remitting: nine years ago (in June 2000) the Medical Advisor to the ME Association wrote in the charity's Newsletter "Perspectives": "***The ME Association receives far more complaints about graded exercise regimes than any other management issues. Consequently, we are now informing our members that they should consider taking legal action against the health professionals concerned when an inappropriate 'exercise prescription' causes a relapse***".

In a keynote lecture at the ME Research UK international research conference held on 25th May 2007 in Edinburgh, Dr Eleanor Stein from Canada, a psychiatrist with a dedicated ME/CFS practice, denounced the Oxford criteria, which she said *"could describe almost anybody. I do not believe that studies which use the Oxford criteria can be generalised to patients with ME/CFS".* She also said it is very clear that ME/CFS patients have "*a host of physiological abnormalities that cannot be explained by psychiatric, attitudinal or behavioural hypotheses".* Stein was outspoken: "***I would never in my practice use the Wessely model of cognitive therapy. I find it disrespectful to try to convince somebody they don't have an illness that they clearly have"****.*

The Canadian Guidelines are rejected by the Wessely School, probably because they do not support the use of CBT/GET: Dr Bruce Carruthers, Fellow of the Canadian Royal College and principal lead of the international expert team that produced the highly respected ME/CFS Clinical Case Definition, states in the Overview (http://www.mefmaction.net/documents/me_overview.pdf):

> *"A hypothesis underlying the use of Cognitive Behaviour Therapy (CBT) for ME/CFS is based on the premise that the patient's impairments are learned due to wrong thinking and 'considers the pathophysiology of CFS to be entirely reversible and perpetuated only by the interaction of cognition, behaviour, and emotional processes. The patient merely has to change their thinking and their symptoms will be gone. According to this model, CBT should not only improve the quality of the patient's life, but could be potentially curative'. Supporters suggest that 'ideally general practitioners should diagnose CFS and refer patients to psychotherapists for CBT without detours to medical specialists as in other functional somatic syndromes'. Proponents ignore the documented pathophysiology of ME/CFS, disregard the reality of patients' symptoms, blame them for their illness and withhold medical treatment. Their studies have often included patients who have chronic fatigue but excluded more severe cases as well as those who have other symptoms that are part of the clinical criteria of ME/CFS. Further, their studies fail to cure or improve physiological impairments".*

At the conference on "CFS" held on 28th April 2008 at The Royal Society of Medicine, PACE Trial Chief Investigator Peter White argued that the less symptoms a definition of "CFS" has, the better. To back up his claim, and using a graph from a study by Simon Wessely, White said: *"You notice a fairly straight line showing the more physical symptoms you have, the more likely you are to meet the criteria for psychiatric distress. The cut-off for CIS* (Clinical Interview Schedule, revised in 1990 by Wessely School psychiatrist Anthony Pelosi) *for psychiatric morbidity is about 12. So once you get above 4 symptoms – you can see once you get 5,6,7,8 symptoms as the Canadian criteria suggest, you are more likely to find someone with a psychiatric disorder and not CFS/ME.* ***So I would suggest you do not use the Canadian criteria****"* (Co-Cure ACT: 1st July 2008).

International ME/CFS experts do not agree with the Wessely School's dismissal of the Canadian criteria.

Although the 9th International Association for ME/CFS Research and Clinical Conference (formerly the American Association for CFS [AACFS] but now the IACFS/ME) held in Reno, Nevada in March 2009 took place after recruitment for the PACE Trial had ceased, evidence pertaining to the PACE Trial was presented by Belgian researchers Drs Greeta Moorkens and Elke van Hoof.

A Report of the conference written by Kim McLeary and Dr Suzanne Vernon from the US CFIDS Association shows that the Belgian research provides yet more evidence of the contra-indication of CBT for ME/CFS:

"*Dr Moorkens reported that the majority of 180 patients treated with 10 sessions of CBT over six months reported some improvement* ***but did not show statistically significant improvement on fatigue or physical functioning scores****. Dr van Hoof confirmed earlier studies that show a high percentage (30%) of drop-outs due to deterioration during CBT trials (and)* ***her studies do not support large scale application of CBT****".* ("ME Essential", Issue 110, Summer 2009, pp 17-19).

At the same Reno conference, Professor Leonard Jason, a world-renowned ME/CFS investigator from De Paul University, USA, reported in his presentation "Activity Management" that one group of ME/CFS patients did not benefit from cognitive behavioural interventions: this was the subset of patients whose laboratory investigations showed them to be the most severely affected and who had increased immune dysfunction and low cortisol levels. This provides ever more evidence of the need for sub-grouping -- a need to which the Wessely School remains adamantly opposed.

In his Statement presented on 28th May 2009 to the US CFS Advisory Committee, the new President of the IACFS, Dr Fred Friedberg, commented on the lack of research into clinical treatment for ME/CFS:

"This is a major concern given these three points: (1) the large number of severely ill and undiagnosed patients, (2) the inadequacy of current subjective diagnostic criteria, and (3) ***the absence of effective, evidence-based treatment options".***

The ME Association's magazine (Issue 110, Summer 2009) carries information on management of ME/CFS based on the findings of the MEA "Big Survey", which is a survey of around 3,500 on-line respondents and 750 paper respondents about management of ME/CFS.

Commenting on the GET aspect of this survey, Professor Christine Dancey from the Chronic Illness Research Team, School of Psychology, University of East London, states:

"There were fewer people who said they were improved than expected. 512 said that GET made them worse, where 302 would be expected if there were no effect of GET. And only 194 said they remained unchanged, when we would expect 302 in this category. ***Based on the results of this survey, GET is a risky strategy****".*

Patients with ME/CFS know this only too well, but their attempts to bring their concerns to the attention of those whose job is to support them constantly fall on deaf ears and blind eyes. It seems that too much is at stake for the plight of patients to take priority over professional reputations and corporate profits.

Professor White's Presentation in Bergen on 20th October 2009

Even after the media frenzy that followed publication of a direct link between the retrovirus XMRV and ME/CFS, Professor White repeated his RSM presentation (see above) virtually unchanged in Bergen, Norway, on 20th October 2009 **and asserted that immune or viral measures are NOT involved in the maintenance of the disorder:**

http://www.meactionuk.org.uk/Bergen-Causes-of-CFS-2009-v2.pdf

http://www.meactionuk.org.uk/Bergen-Treatment-2009.pdf

http://www.meactionuk.org.uk/Bergen-What-is-CFS-2009.pdf

There were also some troubling additions. He said that the risk of major depressive illness in CFS is 7.2% compared with 2.3% in multiple sclerosis patients and he talked about "*endophenotypes*", saying that there are five different endophenotypes: 1.obese & hypnoeic; 2. obese, hypnoeic & stressed; 3. insomnia & pain (myalgia); 4. symptomatic, depressed; 5. symptomatic, depressed, insomnia, stressed and menopausal. How this relates to ME/CFS has not been explained by Professor White.

In Bergen, Professor White said that common factors predispose to all functional somatic syndromes; that CFS is treated *"by helping the patient to remove the barriers to their recovery"*; that CBT and GET are cures in some patients; that the effects of CBT last for five years and of GET for 2 years; that 23% recovered immediately after CBT; that *"those reporting harm with GET had not received appropriately supervised GET and the diagnosis was uncertain*" (a claim which has been demolished by his own studies – see above and BMJ 1997:314:1647-1652); that beliefs and behaviour change with GET; that "*Graded Exposure Therapy changes the brain more than the body"*; that GET changes *"the perception of effort"* which "*normalises with GET"*, and that *"CBT and GET should be offered to all patients".*

Of concern is White's continued insistence that:

- the causes of CFS include female gender, previous mood disorders, childhood trauma and childhood inactivity

- immunisations do <u>not</u> cause CFS (clearly he does not accept the evidence that immunisations may be associated with the development of ME/CFS, for example: Can Dis Wkly Rep 1991:17:215-216; Union Med Can 1993:122:278-279; Lancet Infect Dis 2003:3:709-721; Med Hypotheses 2008: 10th November Epub ahead of print; Autoimmun Rev 2008:8:52-55; furthermore, substantive evidence is held by the Medical Advisor to the ME Association)

- "*maintaining factors"* include mood disorders, illness beliefs, the search for legitimacy, being on benefits, and the diagnostic label

- *"gene expression is highly variable and has not been replicated"*

- **immune or viral measures are <u>not</u> involved in the maintenance of the disorder**,

all of which are astonishing – indeed bizarre -- beliefs and assertions given the amount of evidence that demonstrates compellingly that he and the Wessely School are simply wrong about ME/CFS.

That Peter White should still be so dogmatic in his views is deeply disturbing, especially in the light of the identification of XMRV published in Science online on 8th October 2009 (see also Supporting Online Material: http://www.sciencemag.org/cgi/data/1179052/DC1/1). The full XMRV paper by Lombardi et al was published on October 23rd (http://www.sciencemag.org/cgi/content/abstract/326/5952/585).

White's assertion that "*Immune or viral measures are <u>not</u> involved in the maintenance of the disorder"* would seem to be a direct denial of the evidence of two of the world's leading immunologists who specialise in ME/CFS, Professors Mary Ann Fletcher and Nancy Klimas, who recently published yet more confirmatory evidence of immune dysfunction in the maintenance of the disorder (Journal of Translational Medicine 2009:7:96: doi:10.1186/1479-5876-7-96), and whose peer reviewed article was published immediately upon acceptance.

Fletcher and Klimas et al are clear that cytokine abnormalities are common in (ME)CFS and that the cytokine changes observed are more likely to be indicative of immune activation and inflammation, rather than specific for (ME)CFS, as people with fibromyalgia, Gulf War Illness, rheumatological disorders and multiple sclerosis may also have similar cytokine patterns.

The authors do, however, demonstrate that several of the abnormal cytokines show promise as potential biomarkers for (ME)CFS.

As Fletcher and Klimas et al point out:

"*CFS studies from our laboratory and others have described cytokine abnormalities. Other studies reported no difference between (ME)CFS and controls. However, methodologies varied widely and few studies measured more than 4 or 5 cytokines. Multiplex technology permits the determination of cytokines for a large panel of cytokines simultaneously with high sensitivity.*

"In this study, 10 of 16 cytokines examined showed good to fair promise as biomarkers. However, the cytokine changes observed are likely to be more indicative of immune activation and inflammation…Many of the symptoms are inflammatory in nature.

"There is a considerable literature describing immune dysfunction in (ME)CFS.

"The goal of this study was to determine if, using new technology, plasma cytokines had sufficient sensitivity and specificity to distinguish (ME)CFS cases from age-matched healthy controls….Amounts of cytokines in plasma or serum are often below the level of detection in traditional ELISA assays.

"The availability of sensitive multiplex technology permitted the determination of 16 cytokines simultaneously…In the (ME)CFS cases, we found an unusual pattern of the cytokines that define the CD4 T cell.

"Pro-inflammatory cytokines: A significant elevation in the relative amounts of 4 of 5 pro-inflammatory cytokines in peripheral blood plasma of patients with (ME)CFS was found when compared with the controls. In cases, lymphotoxin (LT)α was elevated by 257% and IL-6 by 100% over the controls.

"T_H2 cytokines: Both interleukin (IL)-4 and IL-5 were elevated in (ME)CFS, with the median of IL-4 (being) 240% and of IL-5 (being) 95% higher in cases than controls.

"Anti-inflammatory cytokines: IL-3 was significantly lower in (ME)CFS patients.

"T_H1 cytokines: IL-12 was significantly elevated (120%) and IL-15 decreased (15%) in cases compared to controls.

"IL-8 (CXCL8): this chemokine was 42% lower in the (ME)CFS patients.

"Along with the T_H1 abnormalities, we found up-regulation of T_H2 associated cytokines, IL-4 and IL-5, in the (ME)CFS subjects. Allergy is common in (ME)CFS cases. Years ago, Straus et al reported >50% atopy in 24 CFS patients.

"The probability of chronic inflammation in (ME)CFS patients is supported by the elevation of four members of the pro-inflammatory cytokine cascade , LTα, IL-1α, IL-1β and IL-6, in the (ME)CFS samples compared to controls.

"Interleukin-13, associated with inhibitory effects on inflammatory cytokine production, was lower in cases compared to controls.

"The inflammatory mediator IL-8 (a chemokine known as CXCL8) known to be responsible for migration and activation of neutrophils and NK cells was decreased in plasma of (ME)CFS patients.

*"**The observations of abnormal cytokine patterns in (ME)CFS patients support the reports of retrovirus infections.***

"Recently, DNA from a human gammaretrovirus, xenotropic murine leukaemia virus-related virus (XMRV) was found in the PBMC of 68 of 101 patients compared to 8 of 218 healthy controls. Patient–derived, activated PBMC produced infectious XMRV in vitro. Both cell associated and cell-free transmission of the virus to uninfected primary lymphocytes and indicator cell lines was possible.

"The decreased natural killer (NK) cell cytotoxic and lymphoproliferative activities and increased allergic and autoimmune manifestations in (ME)CFS would be compatible with the hypothesis that the immune system of affected individuals is biased towards a T-helper (T_H) 2 type, or humoral immunity-orientated cytokine pattern.

"The elevations in LTα, IL-1α, IL1β and IL-6 indicate inflammation, likely to be accompanied by autoantibody production, inappropriate fatigue, myalgia and arthralgia, as well a changes in mood and sleep patterns.
"This study is among the first in the (ME)CFS literature to report the plasma profiles of a reasonably large panel of cytokines assessed simultaneously by multiplex technique.

"Cytokine abnormalities appear to be common in (ME)CFS. The changes from the normal position indicate immune activation and inflammation.

"The results imply a disorganised regulatory pattern of T_H1 function, critical to antiviral defence.

"The results from this study support a T_H2 shift, pro-inflammatory cytokine up-regulation and down-regulation of important mediators of cytotoxic cell function".

Since it is unequivocal that people with ME/CFS show markers of inflammation, the PACE Trial (predicated on the assumptions of deconditioing, on the "perception" of effort and on aberrant illness beliefs and whose participants are instructed on "sleep hygiene") cannot but be seen as ill-conceived.

In Bergen, Professor White did, however, mention some interesting facts about the PACE Trial: according to him there are 641 participants; there is a 6% drop-out rate from treatment, and a particular difficulty was that they had trouble recruiting and training new therapists.

Notably, because of participant recruitment problems, the support of the Prime Minister (PM) was sought and the PM --- who is neither a physician nor a medical scientist -- apparently agreed to say: "*As with all serious illnesses, it is important that patients, their families and the healthcare professionals looking after them* ***have the best scientific information available*** *and the PACE trial has been designed to help them decide for themselves what treatment is likely to be the best from* (sic) *them" (*White's slide gave an incorrect URL that was incorrectly copied from the Number 10 website; the correct URL is http://www.number10.gov.uk/Page14656).

Given that the Wessely School does not accept the *"best scientific information available"* about ME/CFS and that PACE Trial participants – some of whom may be as young as 17 – may be so disempowered that they may be unable to *"decide for themselves"*, it can only be speculated who provided the text for the PM.

In his Bergen presentation, Professor White failed to mention what patients think of PACE, which is also on the Prime Minister's website:

"The latest DWP Guidelines and PACE are still directing the Health Service to treat ME sufferers with GET and CBT (a tool used for mental illnesses) despite the mounting evidence from a vast amount of research proving that ME is an organic not a psychosomatic disease and that the treatments forced onto those affected do in fact cause more harm than good and can worsen the condition of patients…Patients should not be forced into becoming psychiatric cases or lose their benefits".

Notably, Professor White said in Bergen that the primary outcomes of the PACE Trial are the statistics on *"**fatigue** and disability"* and – significantly – **that the aim of the PACE Trial is *"Health economics and societal costs"***.

So there we have it: the PACE Trial is not about curing the sick or the advancement of medical science but is indeed about the cost of ***"fatigue"*** to society.

Attention must therefore be drawn to an important paper published in the Annals of General Psychiatry (Psychiatry during the Nazi era: ethical lessons for the modern professional. Rael D Strous, Ann Gen Psychiat 2007:6:8: doi:10.1186/1744-859X-6-8) in which the author not only considers why it was psychiatrists who were most active in playing central and pivotal roles in the Nazi atrocities, but also examines how their transgressions related to a paradigm shift in how patients were viewed:

"Their actions were a colossal misjudgment based on what today we may term 'pseudoscience', but which at the time was deemed to be correct by many…In addition to resting on poor science, the atrocities of the German psychiatric establishment were based upon several fundamental errors of ethical, professional, and scientific conduct. While many may simply brush off any deeper consideration of the issues with the stance that 'they were just evil', such an approach only deepens the risk that such events will be repeated.…Many psychiatrists maintain that they have an inherent responsibility more than other medical professions to be involved in community affairs. This is because psychiatry…often involves taking into account societal factors and contemporary ideology…The dangers inherent in such involvement, while not obvious, are, however, prominent when important boundaries become blurred. Clinical practice and political machinations need to be kept separate…The management of patients must be dictated primarily by the patient's best interests and not by virtue of any ideology that may be prevalent at that time in society. This may include economic 'ideological' considerations…Psychiatrists should be wary of political and economic pressures that

impinge upon medical decisions and health service provision…Science in general and psychiatry in particular needs to be independent from contemporary sociological and political contexts".

Noting that well-developed ethical principles did not stop the trespassing of political ideology into clinical practice and research in the 1930s, Strous concluded: "*A dark side to medicine exists: psychiatry, academia, and science played a key role in the establishment of National Socialism and all that ensued* (see Section 1 above). *The experience of psychiatry during the Nazi era provides an example of how science can be perverted by politics and therefore can become vulnerable to misuse and abuse"* and he warns of *"the very real dangers of the perversion of science and clinical management by outside political influences".*

Given that it has been confirmed by the PACE Trial's Chief Investigator that the aim of the PACE Trial is *"Health economics and societal costs"*, is it the case that "*outside political influences"* are the bedrock of this particular MRC trial?

It is undeniable that the Wessely School persistently ignore the large body of biomedical evidence that does not accord with their own beliefs about the nature of ME/CFS, and this is one of the central arguments against the PACE Trial. Another central argument is the denial of adequate investigations for people with ME/CFS: if there is no desire to find the cause of a disease, or its cure, then do not look for it; such a stance, however, is not in the best interests of either medical science or society as a whole.

Since the general body of knowledge known about by other clinicians and researchers working in the field of ME/CFS is now so great, the question repeatedly asked is: at what point will that body of scientific knowledge be so great that it will be considered serious professional misconduct to ignore it and to continue to deceive patients by pretending that it does not exist?

It is important to be aware of the press release from Professor Maes and Frank Twisk that accompanied their review (referred to above) in which the authors said:

"*There is now sufficient evidence that ME/CFS is a disorder that primarily involves an inflammation with dysregulated and suppressed immune functions, oxidative stress, infections, autoimmunity and mitochondrial dysfunction. During the last few years, many scientific studies, including gene expression research, have confirmed that patients with ME/CFS suffer from the above….Despite major scientific breakthroughs, ME/CFS is still described in the popular media as a medically unexplained disorder. Cognitive behavioural therapy and graded exercise therapy are declared to be the only possible therapies. A thorough analysis of the current medical (and) scientific literature and international patient surveys, however, show that CBT/GET is not only ineffective for the majority of ME/CFS patients, but also potentially very harmful…inflammation, oxidative stress and dysfunctional ion channels will be amplified by minor exertion and by 'rehabilitation therapies' like CBT/GET. The reviewers urge policy makers to change their policies by putting a stop to potentially harmful and ineffective 'rehabilitation' programmes, and investing into medical research and therapies targeted at the immune system, infections and other pathological aspects of this disease"*
(http://www.ediver.be/ediver/latest%20news/PRESS%20RELEASE%20CBT%20and%20GET%20in%20ME%20CFS.pdf).

<u>Defiance of science is rewarded in the UK</u>

Many people (including Professor Martin Pall – see above) have openly queried how it is possible for the Wessely School model of "CFS/ME" to have gained such popularity and even credibility. It is worth re-visiting what Pall said in his book "Explaining 'Unexplained Illnesses' ":

"One of the great puzzles about the psychogenic literature regarding these multisystem illnesses is how do so many bad papers get published? How do so many papers dominated by emotion laden phrases, by transparent falsehoods, by logical flaws, by overstated claims and by unsupported or poorly supported

opinion get published in what appear to be respectable, peer-reviewed journals? These papers consistently ignore massive amounts of contrary data and opinion and cannot, therefore, lay claim to objective assessment of the literature. .. This is by far the largest failure of the peer-review system that I am aware of. I am almost tempted to call this failure inexplicable…I can't help speculate on…the abject failure of the psychogenic advocates to uphold even the minimum of scientific standards".

In what is regarded by many people as a medico-political scandal of immense magnitude, for what is deemed to be their *"abject failure to uphold even the minimum of scientific standards"* the Wessely School have been lauded and honoured by those who share their beliefs.

As noted above, in 2004 Peter White was awarded an MBE for his work on CFS, the citation being "*For services to medical education".*

On 27th August 2003, Professor George Szmukler, Dean of the Institute of Psychiatry (who has co-authored papers with Simon Wessely's wife), wrote to the Countess of Mar about Simon Wessely in the following terms:

"I would like to say a few things about Professor Wessely. Questions about CFS/ME should be resolved through research, with rigorous scrutiny of the methods, findings and conclusions by the community of scientists devoted to the field. By these standards, Professor Wessely must be judged one of the outstanding medical researchers in the UK, and indeed internationally. His research has been regularly and continuously funded by bodies such as the Medical Research Council and the Wellcome Trust which exercise the most demanding levels of peer review. Similarly, the publication of Professor Wessely's research findings has consistently and predominantly been in journals in which submissions are again subject to the most exacting scrutiny by his scientific peers. Professor Wessely has been awarded a Research Medal by the Royal College of Physicians (specifically for work on CFS) and he has served on many prestigious scientific committees further attesting to the high regard in which he is held by the scientific community" (http://www.meactionuk.org.uk/Mar_Szmukler_Correspondence.htm).

On 16th October 2009, the President of the Royal College of Psychiatrists, Professor Dinesh Bhugra, announced that The Psychiatric Academic Award of the Year had been presented to Professor Michael Sharpe "*for his dedication to enhancing psychiatry's relevance and reputation amongst medical colleagues, and mentoring the next generation of psychiatrists".* Professor Simon Wessely was a short-listed nominee. Professor Bhugra said: "*On behalf of the College, I want to congratulate all this year's winners and shortlisted nominees".*

Such self-serving awards to these psychiatrists – from people within their own circle who encourage and support each others' activities -- seem to ridicule and even to obliterate the profound, continuous suffering of people with ME/CFS. Is it any wonder that so many people with ME/CFS are driven to suicide?

That the Wessely School has been inordinately successful in disseminating their own beliefs about ME/CFS, cannot be in doubt. On 2nd February 2010 The Guardian carried a feature by "Dr Crippen" in which he commented scathingly about the assisted suicide of severely-affected ME patient Lynn Gilderdale, referring to ***"myalgic encephalomyelitis"*** disparagingly in inverted commas as ***"a condition that many doctors only recognise as an inappropriately named psychiatric illness"***.

Responding to his critics, on 3rd February 2010 "Dr Crippen" wrote: "*Yes, some doctors have closed their minds to the condition; the main problem is that the militant ME brigade…will not listen to any opinion other than the one that entirely agrees with their own. They stand like children, with their fingers firmly in their ears shouting 'la la la la la la' until everyone else stops talking. Thus they bring the whole condition into disrepute".*

This drew many notable responses including: "*It is doctors with false illness beliefs (who) stand like children, with their fingers in their ears shouting 'la la la la la la' until everybody else stops talking (who) bring the whole condition into disrepute"* and one that referred to *"a herd-like mentality among doctors who are more interested in how they appear to their colleagues…than in doing the right thing by their patients".*

SECTION 3: Consideration of the MRC PACE Trial

Under "Topic" in the UK Clinical Research Network Study Portfolio, the PACE Trial is listed as "Neurological"; the category of disease being studied is listed under "Nervous system disorders"; under "Main Inclusion Criteria" is stated "Unknown" and under "Main Exclusion Criteria" is also stated "Unknown", which may reflect the fact that Peter White sought approval from the West Midland MREC to write to GPs virtually imploring them to send anyone with "*chronic fatigue (or synonym)"* for entry into the PACE Trial, thereby opening the trial to anyone who is simply tired all the time (TATT).

Furthermore, a recent letter from Jane Spencer at the Department of Health (the DoH being a co-funder of the PACE Trial) states:

"*The Department of Health accepts CFS/ME is a chronic long-term neurological condition of unknown cause and health and social care professionals should manage it as such.*

"No management approach to CFS/ME has been found to be universally beneficial and none can be considered a cure.

"As with any treatment, an explanation of the benefits and possible harmful effects of CBT should always be provided before decisions are made to offer and accept treatment"
(http://www.facebook.com/edittopic.php?uid=154801179671&topic=10499&action=4#/topic.php?uid=154801179671&topic=10550).

This is notable, because the PACE Trial Principal Investigators consider "CFS/ME" to be a condition of medically unexplained fatigue and deconditioning that is perpetuated by "*inappropriate illness beliefs*", neither do they accept that CBT/GET has any harmful effects and indeed, PACE Trial participants are specifically reassured that such is the case (see below).

The same letter from Jane Spencer at the DoH also states:

"*The main agency through which the Government supports medical and clinical research is the Medical Research Council (MRC).*

"It maintains a rigorous decision-making process and only funds research that is likely to make a significant contribution to knowledge and is a good use of tax-payers' money. Decisions to support proposals are taken on the grounds of scientific quality and whether the research proposed would be likely to inform the knowledge base. There is certainly no bias….

"Both trials (PACE and FINE) ***were subject to rigorous peer review that ensured their methodology was robust"***.

Information obtained under the FOIA and scrutiny of the trial literature appears to cast serious doubt on such assertions and may invalidate them.

Misinformation in the MRC PACE Trial literature

The Patient Clinic Leaflet (http://pacetrial.org/trialinfo.html) that encouraged patients to become PACE Trial participants states: *"Chronic fatigue syndrome"* is *"also known as post-viral fatigue syndrome, myalgic encephalomyelitis (ME) or myalgic encephalomyelopathy (ME)"*, thus there can be no doubt that patients with the neuroimmune disease ME are alleged to be included in the PACE Trial. Whether or not it can be verified that such patients were in fact recruited has not yet been clarified, since the entry criteria (the Wessely School's own 1991 "Oxford" criteria) specifically exclude those with a neurological disorder.

The same leaflet also states: ***"Medical authorities are not certain that CFS is exactly the same illness as ME, but until scientific evidence shows that they are different they have decided to treat CFS and ME as if they are one illness***".

This is a seriously misleading statement, because the Wessely School do not distinguish between the Chronic Fatigue Syndrome (CFS), myalgic encephalomyelitis (ME) and chronic fatigue (CF) and they ignore the international research showing that ME/CFS (ICD-10 G93.3) is not the same as "chronic fatigue" (ICD-10 F48.0). It seems that no matter how extensive the existing evidence, the Wessely School will continue to dismiss and/or ignore it because it does not accord with their own agenda of eradicating ME and reclassifying "CFS" (by which they mean medically unexplained chronic "fatigue") as a behavioural disorder.

To combine different disorders -- a neurological disease (ME / ICD-10 G93.3), a soft tissue disorder (FM / ICD-10 M79)) and a somatisation disorder (chronic "fatigue" / ICD-10 F48.0) -- and then to regard and manage them as a single psychiatric disorder is a cause for concern because interventions that may be suitable for those with "chronic fatigue" may be harmful and even fatal for some with ME.

That such a failure to differentiate between disparate disorders runs throughout the PACE Trial is shown by a job advertisement placed by the Oxford Radcliffe Hospitals NHS Trust (one of the PACE Trial participating Centres) for a Research Cognitive Behaviour Therapist, which said:

"This is a unique opportunity to learn specialised treatment skills and to participate in a high profile Medical Research Council funded treatment for patients with chronic medically unexplained fatigue (CFS/ME)".

ME/CFS is not "*chronic medically unexplained fatigue*" but a classified nosological entity in which the pathognomonic feature is post-exertional fatiguability, not "fatigue" which equates to "tiredness".

The nub of the problem lies in the criteria used to define "CFS/ME" in the PACE Trial, and indeed in all the trials concerning behavioural interventions for "CFS" published by the Wessely School to date. On 20th May 2009, a letter to the New Scientist from Jennifer Wilson summarised the problem:

"*In most studies into the efficacy of cognitive behavioural therapy (CBT) and graded exercise therapy (GET), the people who report in favour of the treatments most likely do not have, nor ever had, ME. They are likely to be suffering from psychological chronic fatigue, which is very different. The inclusion of people with chronic fatigue in research into ME muddies the waters. ME sufferers cannot undertake exercise - not even graded exercise - without worsening their illness. Some of the criteria for including people in studies on CBT/GET exclude the very markers that show someone has ME, such as the very distinctive symptom of post-exertional malaise. Reported success stories highlight not those with ME, but sufferers of the entirely different illness, chronic fatigue"* (accessible at http://www.newscientist.com/article/mg20227090.500-confused-over-me.html).

When the Wessely School refers to "evidence-based medicine" (EBM) in this context, they are referring to the reportedly positive findings in certain controlled trials of cognitive behavioural therapy (CBT) and graded exercise therapy (GET) aimed at increasing a "CFS/ME" patient's activity level. However, the recruitment criteria which they use to identify patients with "CFS/ME" are their own and are not used by most international researchers: they are regarded as obsolete by medical scientists; they lack diagnostic specificity and select a heterogeneous patient population, thus their results lack meaningful scientific interpretation.

As the Wessely School ignore all the clinical signs and much of the key symptomatology of ME/CFS, focusing on subjective "fatigue", their data-set cannot be representative of ME/CFS patients, yet they repeatedly claim to include and study those who suffer from ME under their own umbrella of "medically unexplained chronic fatigue"; however, they do not study people with other discrete neurological disorders

such as multiple sclerosis in which fatigue is a major feature, so their purloining of just one classified neurological disorder (ME) is particularly notable.

One of the MRC PACE Trial Principal Investigators (Michael Sharpe) and the person who will oversee the PACE Clinical Trial Unit (Simon Wessely) were involved in the formulation of the Fukuda et al CDC 1994 criteria: Sharpe was a co-author and Wessely was a member of the "International Chronic Fatigue Syndrome Study Group", and they successfully incorporated elements of the Wessely School beliefs into the CDC 1994 definition. For example:

"We dropped all physical signs from our inclusion criteria"

"Whether to retain any symptom other than chronic fatigue generated the most disagreement among the authors"

"***We did not use other psychiatric disorders, such as anxiety and less severe forms of depression, as a basis for exclusion…..The exclusion of persons with these conditions would substantially hinder efforts to clarify the role that psychiatric disorders have in fatiguing illness***" (Ann Intern Med 1994:121:12:953-959).

This means, of course, that the CDC 1994 criteria do not specifically identify those with ME and they lend legitimacy to the hijacking of the term "CFS" by the Wessely School to include those with non-organic fatigue.

Recruitment to the PACE Trial

It is enlightening to note the tactics used to secure patient recruitment and to retain their participation, about which the Institute of Psychiatry's Clinical Trials Unit document "Patient Recruitment" (accessible on the IoP's website) is informative:

"Patient recruitment is …one aspect of a trial that we cannot easily control. Active participation of consumers/users/clients/patients, whatever one chooses to call them, is vital if any clinical trial is to be brought to a successful conclusion".

The IoP CTU document draws attention to various bodies that have been set up specifically to develop *"strategic alliances"* with key groups in order to promote greater involvement in clinical trials and it notes: "*Consumers can help with recruitment of their peers"* and that they can *"disseminate the results…to ensure that changes are implemented"*, observing that ***"The involvement of consumers is now becoming an increasingly political priority".***

The IoP's CTU "Recruitment Checklist for Large Clinical Trials" includes the following:

"At the protocol and funding stage:

- *Choose a good acronym*
- *Budget for marketing costs, such as newsletters, headed notepaper etc*
- *Develop partnerships with consumer groups*

"At the start-up and recruitment stage:

- *Choose a striking logo, and put it onto letterheads and all trial materials*
- *Write articles for medical journals and consumer conferences*
- *Present papers and posters at relevant conferences*
- *Provide user-friendly, attractive and stylish trial materials*

- *Consider a 24-hour on-call service for dealing with trial queries*
- *Consider a launch meeting for collaborators*
- *Consider a dedicated trial website, it could include all trial materials, information leaflets etc*

"To maintain recruitment:

- *Circulate regular newsletters with updates on progress*
- *Use posters or letters of congratulation to acknowledge good progress*
- *Consider offering incentives for achieving targets, such as T-shirts, mugs or pens etc*
- *Use opportunities to 'piggy-back' small meetings onto national or international conferences.*

The choice of the acronym "PACE" seems particularly misleading because some participants may have thought the trial was about "pacing" when it seems not to be – it is about restructuring participants' cognitions by means of CBT and about reversing "deconditioning" by means of GET and even by APT (which, in the PACE Trial, requires participants to plan and practise activity and relaxation according to a timetable), all of which are referred to in the trial literature as forms of "pacing" when they clearly have little in common with "pacing" that is defined as "listen to your body" (see below). **The use of acronyms that mislead people is a tactic that may be considered a form of coercion** (Chest 2002:121:2023-2028).

It is notable that there is considerable effort being invested in ensuring that trial participants remain engaged with and do not withdraw from the trial; a recent paper co-authored by Alison Wearden (FINE Trial Investigator) highlights the net-working that is employed by those using CBT in particular:

"*Orne and Wender (1968) first suggested that an important factor in the success or failure of therapy is the degree to which patients understand what they called 'the rules of the game'.* ***They suggested that 'anticipatory socialisation' would increase the benefit from therapeutic input…(and that it) would be an important condition for success in any type of psychotherapy****…Walitzer et al (1999) suggest* ***that cognitive behavioural therapists would benefit from the systematic use of these strategies to enhance engagement and promote positive outcome*** (see below for how reinforcement of "positive outcome" is utilised in the PACE Trial). *Beck (1995) recognised the importance of socialisation in maintaining…patient engagement, outlining that therapists need to 'sharpen their skills at socialisation'. Beck offered a 27-point checklist of <u>how</u> to socialise the patient to cognitive therapy (and) the therapist can use the checklist to determine whether the patient is sufficiently socialised.* ***Wells (1997) referred to socialisation as 'selling the cognitive mode****l'…The present operational definition can be used to clarify a concept in frequent use in clinical psychology (and) may influence clinical practice by defining the main components that can guide clinicians to socialising the patient adequately …to cognitive therapy"* (Jo Roos and Alison Wearden. Behavioural and Cognitive Psychotherapy 2009:37:341-345).

This background seems to provide the rationale for the emphasis on "empathy" with participants (for example, the sending of birthday cards to them and encouraging them to provide positive contributions to the PACE Trial Newsletters, thus ensuring their "involvement") and the emphasis on "positive reinforcement" that permeate the PACE Trial literature, all of which are designed to achieve the desired outcome of the trial and may thus be deemed to be misleading participants.

Despite claims that the PACE Trial is *"the largest trial of treatments for CFS/ME to date"* (http://www.iop.kcl.ac.uk/departments/?locator=355&project=10068), the PACE Trial Investigators struggled to meet the target quota to the extent that they changed the eligibility criteria once the trial was underway.

The companion MRC FINE trial (Fatigue Intervention by Nurses Evaluation) ended recruitment in November 2007, with just 296 participants recruited (449 patients having been referred).

According to the PACE Participants' Newsletter Issue 1 (June 2006), after two years of recruiting, *"By May there were 92 people receiving treatments as part of PACE".* Issue 2 (March 2007) states: "*The number of CFS/ME patients recruited to PACE rose steadily to 180 by the end of November 2006"*, which was no-where near the target

of 600 participants. Issue 3 of December 2008 states that numbers of recruits had still not reached the target, so the MRC had granted the Trial team further funding to allow them to continue recruiting until November 2008 to enable them to achieve their target of 600 participants. The PACE Trial Participants' Newsletter Issue 3 said that because there was a problem with recruiting participants, as well as being granted more money by the MRC and more time to achieve the set recruitment levels, it had been decided that an additional Trial Centre should be opened at Frenchay Hospital, Bristol (which had begun recruiting in April 2007).

There was undoubtedly a problem with recruitment and the Minutes of the PACE Trial Steering Committee held on 22nd April 2004 record that recruitment estimates *"need to be reviewed.* ***It was particularly noted that it may be worth training the clinicians who would be recruiting patients into the trial in recruitment strategies and procedures"*** and that ***"The protocol will be amended accordingly. These include: Consider training participant recruiters".***

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. **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 would seem to indicate that something is seriously wrong with the trial.**

With the aim of improving *"generalisation of our results to a larger number of patients"* as well as improving recruitment, by letter dated 9th February 2006 to the West Midland MREC, Peter White requested changes to the eligibility and primary outcome criteria. He sought permission to change the SF-36 threshold for inclusion (the Investigators were having to turn away patients because they were too well) and he sought permission to include patients who had previously received CBT/GET at non-PACE Trial centres. **What the consequences of allowing an unspecified number of people who had previously received CBT/GET to join the PACE Trial might be was not clarified**.

By letter dated 14th July 2006 to the West Midlands 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 the inclusion of patients with *"fatigue (or a synonym)"* might be is a matter for speculation**.

Quite certainly, such broad canvassing has 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 could be meaningless.**

The PACE Participants' Newsletter (Issue 2, March 2007) was openly soliciting for more participants: "*If you know of any friends or family who suffer from CFS/ME and who might be eligible and interested in taking part in the study and live close enough to one of these centres, please suggest they approach their GP for a referral to a PACE centre".* **The problems with using existing participants to recruit new participants are obvious**.

First, the existing participant might no longer feel inclined to report negative effects and might exaggerate any positive effects because (i) they may feel they have become part of the PACE research team and thus feel a loyalty that could influence how they report their experience and (ii) participants who recruit others are asking them to join in their own experience and thus they assume a burden of responsibility, as a result of which they may be less likely to report 'it was awful' or ' it did not help'. This could render their own subjective data invalid. Furthermore, if a participant knows s/he has persuaded someone else to join the

trial, the recruiting participant might no longer feel s/he had the right to drop out or withdraw consent at any time of their choice.

Secondly, a participant who was recruited by a friend or family might also feel similar obligations of loyalty to their friend or family member, so their own data might also be unreliable.

Thirdly, only participants who are enjoying or benefiting from their participation are likely to have recruited others, with the result that a potential participant is exposed to a positive viewpoint that might not adequately reflect the risks and burdens of participation, as well as arousing fears that they are missing out on something helpful. This could be viewed as making unjustifiable claims about the therapies on trial (which could be in breach of the GMC's Guidelines for Good Medical Practice (section 61) that states: *"You must not make unjustifiable claims about the quality or outcomes of your services in any information you provide to patients. It must not…exploit patients' vulnerability or lack of medical knowledge"*).

Fourthly, participants who do not recruit anyone might be influenced by the suggestion that they <u>should</u> recruit and may feel guilty if they are unable to recruit more participants, with the result that they may compensate by being 'better' (ie. more positive and less critical) participants. This could affect they way they report their experience and thus invalidate their data.

Other institutions concerned with research integrity require approval for <u>all</u> methods of advertisement prior to use and they consider *"advertising or soliciting for study participants to be the start of the informed consent process…Advertisements must be reviewed and approved…When advertising is to be used, the information contained in the advertisement and the mode of its communication (must be reviewed) to determine that the procedure for recruiting participants is not coercive and does not state or imply a certainty of favourable outcome"* (http://orip.syr.edu/sop/sop036.php).

The tactics used for recruitment to the PACE trial seem to indicate the difficulties encountered by the Investigators, a fact that is believed by many people ought to have raised concern with the various ethics bodies.

It is believed that the difficulty in recruitment may have resulted in coercion of sick people.

<u>Coercion to take part in the MRC PACE Trial?</u>

Dr Gabrielle Murphy, co-author of the PACE Manual for doctors on Standardised Specialist Medical Care, is also co-author of a book published on 30th September 2009 ("Coping Better with CFS/ME: Cognitive Behaviour Therapy for CFS/ME", Karnal Books, £14.99), the Foreword of which by Professor Robert Bor, Lead Consultant Clinical Psychologist at the Royal Free Hospital where Dr Gabrielle Murphy works, states:

"*By working systematically through the exercises in the book, readers can expect to gain further insight into their condition as well as confidence in managing* ***and overcoming*** *it. They can do so in the knowledge that the ideas come from a sought-after clinical centre and are based on the most useful and modern approaches…It conveys the positive message that patients suffering from CFS/ME can enjoy better physical and mental health".*

Gabrielle Murphy's co-author is Dr Bruce Fernie, a chartered counselling psychologist also at the Royal Free Hospital, whose research interests lie in procrastination, not in ME/CFS.

Not only does Professor Bor's Foreword seem to indicate a disturbing lack of insight and knowledge about ME/CFS, but it seems that the "*sought-after centre*" is to be closed, possibly because it may be thought to have served its purpose in recruiting participants attending its Fatigue Service for the PACE Trial, although this is not the explanation for closure that is being proffered.

Dr Gabrielle Murphy is/was part-time Clinical Lead of the Royal Free Hospital's Fatigue Service; in her absence, the person in overall charge is/was Professor Peter White from St Bartholomew's Hospital, the PACE Trial Chief Investigator.

Less than one month after publication of the NICE Clinical Guideline CG53 on "CFS/ ME" in August 2007 (which states that if a "CFS/ME" patient declines CBT and GET, such patients should not be discharged from medical care), patients at RFH believed the Royal Free Fatigue Service Clinic to be implementing a policy that refused and denied them access to a physician at the clinic unless they agreed to take part in a CBT/GET regime, correctly assumed to be the PACE Trial (this was subsequently confirmed by Dr Gabrielle Murphy herself).

After attention was publicly drawn to this Royal Free Hospital policy in the document "Coercion as Cure?"(21 September 2007: http://www.meactionuk.org.uk/COERCION_AS_CURE.htm), one of the authors was contacted by The Royal Free Hampstead NHS Trust which alleged defamation by the authors. An exchange of correspondence ensued, culminating in the authors' detailed and referenced rebuttal of the allegations of defamation, which the Royal Free Hampstead NHS Trust did not deny. This rebuttal is attached as Appendix II.

On 10th October 2003 it had been confirmed by Dr Gabrielle Murphy that the "CFS" Clinic at St Bartholomew's Hospital (Barts) was no longer an immunology clinic but a psychiatric unit (http://health.groups.yahoo.com/group/MEActionUK/ message 15999), and as The Royal Free Fatigue Clinic is essentially a satellite clinic which comes under the control of Professor Peter White, it was perhaps unsurprising if its policy was that patients who declined to participate in one of the therapies offered by the Clinic (CBT and GET) would be discharged from the Clinic and would have no further access to a doctor for medical advice (access which, apart from any symptomatic medical care, they might need in order to support their claim for state benefits, as a GP cannot endorse a patient's Disability Living Allowance application). However, a GP could re-refer a patient to the clinic if thought appropriate.

Faced with the option of an inappropriate intervention or no intervention plus no further access to a Clinic doctor, a patient may consent to an inappropriate intervention, but is this true consent and may it amount to coercion?

In their paper "Clarifying confusion about coercion" (Hastings Centre Report 2005: 35:5), Hawkins and Emanuel state: "***if a physician-researcher threatened to abandon a patient or withhold necessary standard treatment unless the patient joined a study, this would clearly be coercion***".

The also state: "*Everyone knows that coercion is bad after all; if a practice is coercive then plainly it should be stopped, and the 'coerced' decisions should be set aside (otherwise) we may be led to faulty conclusions and faulty recommendations for change"* and they continue: "***Coercion depends on…the purposeful actions of others that have created that situation…Coercion subverts real choice***".

The matter of apparent coercion in relation to the MRC PACE Trial is a material concern. As noted above, in the absence of the part-time Clinical Lead at the Royal Free Fatigue Services Centre (Dr Gabrielle Murphy), the person in overall charge is Professor Peter White.

If Professor White was recruiting patients attending the Royal Free Fatigue Service Clinic to the PACE Trial on the basis that non-compliers would be discharged from the Clinic raises the possibility that he was recruiting only CBT-compliant patients to his MRC trial, which would decrease the number of trial drop-outs at a stroke, and this would be to his advantage.

Any kind of coercion of sick people is a serious matter. Thomas Schramme, for example, is explicit:

*"An important condition of a justified psychiatric intervention is the informed consent of a patient…**The formal acquiescence of a patient is not a sufficient criterion of informed consent**".*

Schramme continues: "*Even if someone is not physically forced to choose to act in a certain way, he may nevertheless not actually wish to act in this way….Because of an offer, he does something he does not identify with (and) many offers – at least in some contexts in psychiatry—can be regarded as morally dubious"* (as, perhaps, an ME/CFS patient having to choose between the loss of necessary access to a clinician at a "CFS" Clinic unless s/he agreed to take part in the MRC Trial of CBT/GET).

Schramme says: "*offers that are directed against the will we may refer to as cases of manipulation**…..I would like to suggest that an offer is irresistible when it exploits dependency".*** **He then gives the example of refused benefits becoming a threat or, at the very least, coercion, leaving a patient without a real choice**. (Coercive Threats and Offers in Psychiatry. In: Thomas Schramme and Johannes Thome (eds). Philosophy and Psychiatry. De Gruyter 2004:357-369).

Orlowski and Christiensen use the term "coercion" to include subconscious or subliminal pressure to choose to act:

"*Anything that unfairly entices or forces a research subject to participate in a clinical research trial is prohibited by various national and international research codes of ethics, including the Belmont Report and The Nuremberg Code. The Nuremberg code states as its first principle that: '**The voluntary consent of the human subject is absolutely essential. This means that the person involved should …be so situated as to be able to exercise free power of choice without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion**' ".*

Orlowski and Christiensen regard coercion as ***"anything that would impede the exercise of the free power of choice, especially overt or covert enticement"*** (again, the issue of an ME/CFS patient having to choose either the loss of access to a clinician at a "CFS" Clinic or agreeing to take part in CBT/GET springs to mind).

Orlowski and Christiensen quote the Belmont Report on Ethical Principles: "***This element of informed consent requires conditions free of coercion and undue influence"***.

They draw attention to the Council for International Organisations of Medical Sciences' International Ethical Guidelines which, in the section titled "*Obligations of Investigators Regarding Informed Consent"*, state that the Investigator has a duty to *"…**exclude the possibility of unjustified deception"*** (Chest 2002:121:2023-2028).

Concerns about coercion in the PACE Trial continue to mount, because coercion is one of the ways that consent can misfire and research trial Investigators are obliged to ensure that subjects' participation is not secured by coercion or misrepresentation (see below for examples of apparent misrepresentation that seem to have occurred in the PACE Trial).

In "Undue Influence as Coercive Offers in Clinical Trials", Joan McGregor, Lincoln Professor of Bioethics, Arizona State University; Professor of Basic Medical Sciences and Director of Biomedical Ethics and Medical Humanities, speaks with authority:

"*Coerced or deceived consent does not respect the subject's freedom to decide on his or her own what risks to assume….**Informed consent is undermined when there is coercion or 'undue influence'**…..Vulnerable populations can include…those vulnerable because of their circumstances….Their consent to participate may be less than fully voluntary because…of their lack of alternatives…The Common Rule specifies that the researcher must guard against coercion and undue influence (I would include deception as well) since they can affect the voluntariness of the agent, thereby vitiating informed consent…Coercion is a central issue in moral, political and legal philosophy because it undermines the freedom of the victim by making his or her consent invalid…**Coercers ensure that their victims 'choose' the option that the coercers want (in that) the victim must 'choose' the lesser of two evils**…Clinical*

trials…are open to the charge of exploiting the vulnerable by taking advantage of their lack of options and their dependency on researchers for medical care…" (http://www.springerlink.com/content/ph8032w107213410/).

Moreover, calling one arm of the trial "SSMC" (Standardised **Specialist Medical Care**) seems potentially coercive because it gives the impression that participants will be receiving specialist medical care (ie. the best medical care available), which clearly is not the case: "SSMC" may consist of doing nothing at all apart from general advice from a doctor at a Fatigue Service Clinic on balancing activity with rest.

Quite certainly, the West Midlands Multi-centre Research Ethics Committee wrote to Peter White on a number of occasions expressing concern that the wording of the Patient Information Sheet was potentially *"coercive"*; he argued that it was not, but eventually he agreed to modify the wording. That it should have been deemed by the West Midlands MREC to be *"coercive"* in the first place is disturbing.

PACE Trial entry criteria

The entry criteria for the MRC PACE Trial are the Wessely School's own criteria (Oxford 1991).

This is remarkable, given that one of the Principal Investigators himself stated in 1997 that the Oxford criteria *"have been superseded by international consensus"* (Chronic fatigue syndrome and occupational health. A Mountstephen and M Sharpe. Occup Med 1997:47:4:217-227).

However, contrary to accepted scientific practice, those superseded criteria were deliberately chosen in order to enhance applicability to as large a number of "fatigued" people as possible and thus to enhance recruitment to the trial.

The Trial Identifier states at section 3.6:

"*Subjects will be required to meet operationalised Oxford criteria for CFS. This means six months or more of medically unexplained, severe, disabling fatigue affecting physical and mental functions.* ***We chose these broad criteria in order to enhance generalisability and recruitment".***

Deliberately to broaden entry criteria for a clinical trial so that they include patients who do not have the disorder in question would seem to contravene elementary rules of scientific procedure.

As noted throughout this Report, **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.

No researcher hoping for scientifically valid results would choose inclusion criteria based on the desire for enhanced recruitment to the trial, nor would s/he allow broad inclusion criteria for "*generalisability"* if this meant that specificity was destroyed, thus rendering the data imprecise and effectively meaningless.

McGee et al recommend that:

"*Authors should define the population to whom they expect their results to be applied"* (BMJ 1999:319:312-315).

Given that the PACE Trial claims to be studying people with ME, yet includes participants who are simply fatigued, not only is generalisation impossible, but it could be potentially dangerous in view of the known adverse effects of the interventions on those with ME/CFS.

Furthermore, the Chief Investigator (Peter White) himself has previously acknowledged that the Oxford criteria *"allow co-morbid mood disorders".*

He even warned that his own data *"suggest that the Oxford criteria should be used with caution"* when attempting to distinguish between CFS and mood disorders (Lancet 2001:358:9297:1946-1953).

Six years earlier, White stated:

"…the complaint of post-exertional physical fatigue may help to differentiate post-viral fatigue states from psychiatric disorders…<u>This study provides evidence that previous definitions have been over-inclusive, and that the post-viral fatigue syndrome is probably not a misclassified psychiatric disorder</u>…This is the first clinical evidence to suggest that a postviral fatigue syndrome is a discrete, valid and reliable condition. This supports the differentiation found with endocrine measures in the chronic fatigue syndrome" (Psychological Medicine 1995:25(5):917-924).

On what rational basis, therefore, does White – as Chief Investigator – now disregard his own previous research evidence that ME/CFS is <u>not</u> *"a misclassified psychiatric disorder"*?

Also in 1995 White further stated:

"***The Oxford criteria are more widely defined…(and) allow the inclusion of affective illnesses****….There are marked discrepancies between the empirical syndrome* (White's own empirical definition of a post-viral fatigue syndrome following glandular fever: Psychol Med 1995:25(5):917-924) *and descriptions of myalgic encephalomyelitis.*

"These descriptions included physical symptoms which are not found in our syndrome, such as tinnitus, dysequilibrium, hot flushes and myalgia*. Descriptions of epidemic outbreaks of myalgic encephalomyelitis are even more discrepant because of their frequent inclusion of muscle 'paralysis', headache and muscle pains.*

"These discrepancies may be because myalgic encephalomyelitis is a different illness"(Psychol Med 1995: 25(5):907-916).

Given that White is aware of cardinal differences in symptomatology between ME and other fatigue states, and that he is also aware that the Oxford criteria do not exclude those with primary psychiatric disorders (as is clear from his series of studies on the same cohort of patients in 1995 which were part of his MD thesis awarded by the University of London -- re-published in the Lancet in 2001:358:9297:1946-1953), it is notable that the Minutes of the Joint Trial Steering Committee and Data Monitoring and Ethics Committee meeting held on 27th September 2004 record:

"Professor Peter White explained the difficulties with selecting diagnostic criteria for CFS/ME, and explained that there had been a certain amount of pressure from the ME Association to use the Canadian criteria over those that had been selected for the study.

"Professor Sharpe went on to explain this, stating that the criteria should be selected for their reliability, validity and feasibility. None of the available criteria can confidently be described as reliable, and therefore criteria have to be selected on the basis of validity and feasibility. In terms of validity, the Oxford or CDC criteria have previously been used in research but not the London or Canadian criteria".

Given that the Oxford criteria (ie. the Wessely School's own criteria funded in part by Peter White himself) specifically exclude those with ME (ICD-10 G93.3) but specifically include those with psychiatric disorder, the criteria that were to be used for the PACE Trial cannot be described as having validity, but it seems that the MRC Trial Steering Committee and the Data Monitoring and Ethics Committee and the West Midlands MREC were uncritical of this important determinant. Moreover, it is scientifically invalid for the Wessely School to assert that the Oxford criteria do not exclude those with ME on the basis that the Wessely School do not accept that ME is a neurological disorder.

It is notable that in 2009, Simon Wessely wrote with approval of the need for homogeneity in clinical trials, citing a 1923 paper: "*Because of the difficulties of interpretation inherent in an investigation of this nature, it seemed desirable to reduce the study as nearly as possible to the terms of the experiment.* ***Consequently, all patients were divided into two groups as nearly identical as possible***" (Wessely S. Surgery for the treatment of psychiatric illness: the need to test untested theories. www.jameslindlibrary.org).

On what credible basis, therefore, do those involved with the MRC PACE Trial disregard this well-established scientific precept for the need for clinical trial participants to be as identical as possible?

The PACE Trial Investigators have intentionally mixed at least three taxonomically different disorders in the trial cohort -- 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).

A comment by GR of the UK (one of 69) in the Mail Online on 10th October 2009 is apposite: "*To include those with no underlying organic disorder with those who do is a recipe for disaster*" (http://www.dailymail.co.uk/health/article-1219207/Chronic-fatigue-caused-retrovirus-say-scientists.html).

The MRC was asked more than once how such heterogeneity could not result in skewed and meaningless results, but failed to respond.

Selection of PACE Trial participants

Every entrant to the PACE Trial was to commence by seeing a doctor at a "Fatigue Clinic" and the doctor was told what to say to each potential participant. The whole ethos of this MRC PACE Trial may have been biased because it seems that there may have been misinformation provided from the start.

The "Invitation to join the PACE trial" leaflet insisted that participants must be diagnosed with "CFS/ME" only by members of the Wessely School: "*You must be diagnosed* ***by us*** *as having CFS/ME.* ***Fatigue*** *or lack of energy must be your main problem*".

That immediately ought to rule out patients suffering from ME (ICD-10 G93.3), because chronic tiredness or "fatigue" (ICD-10 F48.0) bears no relationship to the post-exertional physiological exhaustion that is the hallmark of ME. "*Fatigue or lack of energy*" would include those with chronic "fatigue" and it is understood that the results of the PACE Trial are to be used to deliver CBT/GET for everyone throughout the UK with a diagnosis of "CFS/ME", which could be detrimental to those with true ME/CFS.

It cannot be emphasised enough that to amalgamate different disorders as a single construct is contrary to the WHO's taxonomic principles, which state that it is not permitted for the same condition to be classified to more than one rubric, and the Wessely School's insistence that ME/CFS has dual classification in the ICD has been conclusively dismissed by the WHO.

Given that participants were carefully selected by the Wessely School themselves (the Trial literature states that people would be selected only if they were deemed *"suitable"* by the Wessely School), it seems that the trial is not "randomised" as claimed by the Investigators – it is only randomised within the trial. Such

selectivity seems not to accord with the advertisement for the PACE Trial that was sent to GPs, which states that 600 patients *"will be recruited **from consecutive new patients** attending specialist chronic fatigue and CFS/ME clinics with a diagnosis of CFS/ME made according to the Oxford research diagnostic criteria"* (this was changed during the life of the Trial).

Furthermore, how can the results of an intervention in any trial be "evidence-based" for efficacy in a disorder when those most severely affected by that disorder are excluded from the outset?

Key people involved with the PACE Trial are known to be "contentious"

As noted above, the three Principal Investigators are Professors Peter White, Michael Sharpe and Trudie Chalder. The PACE Clinical Trial Unit (CTU) is directed by Professor Simon Wessely, who is a member of the Trial Management Group.

It is these people themselves who foster the idea that ME/CFS is "contentious"—the World Health Organisation is not similarly vexed by the nosological status of ME/CFS.

The Institute of Psychiatry's "Your Mental Health" website says on page 18 about "*Chronic fatigue syndrome/ME"*:

"*Developing and testing sometimes controversial treatment programmes*: ***treatment programmes for CFS/ME have attracted controversy over the years…One of the collaborators in PACE is the Chronic Fatigue* (sic) *Research and Treatment Unit based at the IoP…and headed by Professor Trudie Chalder, who says she thinks people's beliefs may have an important part to play in the recovery process…'Beliefs and attitudes towards illness are important in many conditions', she said.'Shifting beliefs that may make recovery more difficult is one of the arms of the cognitive behaviour therapy used within the Unit' "*** (http://www.iop.kcl.ac.uk/iopweb/blob/downloads/locator/l_26_research_report_2008.pdf).

It is notable that documents released under the FOIA provide evidence that the original "Manual of cognitive-behavioural treatment for CFS" dated 19th June 2002 for the PACE Trial was authored by Chalder T, Deale A, Sharpe M and Wessely S. It is further noted that, due to the contention surrounding him, Wessely's name was subsequently removed from authorship, possibly to avoid anticipated difficulties with recruitment, given his indisputable reputation and the evidence of his disbelief in the existence of ME.

Indeed, the Minutes of the APPGME held on 17th May 2007 record that Dr Ira Madan (Director of the NHSPlus Guideline on the "Occupational Aspects of the Management of CFS") informed MPs that she and her group "***deliberately chose not to approach Professor Simon Wessely because they realised his appointment would be contentious***".

The contentious beliefs of Professors Wessely, Sharpe and White about ME/CFS patients speak for themselves (see Section I above and also http://www.meactionuk.org.uk/Quotable_Quotes_Updated.pdf).

The involvement of the charity Action for ME in the PACE Trial

Of note is the fact that the PACE trial was designed in collaboration with the charity Action for ME (AfME).

The PACE Trial Identifier states: "*Mr Chris Clark, CEO of AfME, will be a member of the TMC (Trial Management Committee) and help with external relations*". (Mr Clark left AfME in 2006 and was replaced by Sir Peter Spencer). The Identifier also states: "***Compliance with both the treatments and the study will be***

maximised by the collaboration and support of AfME". "Compliance" and "collaboration" are strong words and they may indicate just how influential was the involvement of AfME in the PACE Trial.

In section 6 ("Application History") the Trial Identifier states at 6.1:

"*A similar application of a much smaller two arm trial (FATIMA; Grant number G9825745) was submitted in full to the MRC in 1999, rated Alpha B, but not funded.*

"The outline proposal of this study (G010039) was approved for a full proposal in October 2001. ***The major innovations in this application include close collaboration with Action for ME****".*

This statement by Peter White indicates that the PACE Trial might not have been funded without the "collaboration" of Action for ME.

By letter dated 6th December 2004 to the West Midlands MREC, Peter White confirmed the involvement of AfME in the PACE Trial Manuals (see Section 4 below): "*The treatment manuals have been developed with the active involvement of the main patient charity, Action for M.E"*. This was a somewhat misleading statement, as the main UK ME charity is the ME Association which has been in existence since the 1970s, whereas AfME was not founded until March 1987.

It is noteworthy that Action for ME, a charity that was set up by ME sufferer Sue Findley as a self-help group for people with ME, has been so influential in supporting and working on a trial that assumes membership of a self-help group to be a predictor of a poor outcome to treatment (Trial Identifier, section 2.3) and with a trial whose Investigators believe AfME's members to be mentally ill.

AfME's members might wish to consider why a charity that was formed to support people with ME should now work so closely in the PACE Trial with those who choose to deny that ME even exists, including the attendees at the Malingering and Illness Deception Meeting in Woodstock, near Oxford, on 6th – 8th November 2001 (see Section I above)**.**

AfME's Principal Medical Advisor has been Professor Pinching (it is understood that he planned to stand down in December 2009). Pinching is well-known for his published view that the Oxford criteria are "*probably too narrow"* (most clinicians specialising in ME/CFS think they are too broad, as they specifically include people with psychiatric fatigue); that over investigation can be *"counterproductive to the management of these patients…. causing them to seek abnormal test results to validate their illness"*; that approaches to symptom control *"can be behavioural or pharmacological"* and that *"The essence of treatment is activity management and graded rehabilitation"* (Prescribers' Journal 2000:40:2:99-106).

As noted in Section 1 above, Pinching is lead advisor to the DoH on "CFS/ME"; he was Chairman of the Investment Steering Group that devised the process and criteria for setting up the 12 "CFS" Clinics throughout the country that are led by "clinical champions"; he oversaw the assessment of bids and allocated the funds (£8.5 million). A further 28 local support teams were set up to provide "*training resources for health professionals*" and to provide "*specialist assessment*" and advice on how to overcome "*too much focus on normal bodily sensations, personality traits, avoidance behaviour and learned helplessness*" (Environmental Issues Forum: Spring /Summer 2004:14-17).

These "CFS" Clinics have been extensively criticised by ME/CFS patients (see www.erythos.com/RiME).

The Wessely School views about "CFS/ME" patients have been crystallised into a Wessely School "CFS profile" as formulated by at least two of the Government-funded "CFS" centres in their job descriptions for candidates who are to deal with "*the undeserving sick*", as PACE Trial Principal Investigator Michael Sharpe refers to them (Lecture given at the University of Strathclyde, October 1999; transcript available). Those advertisements were placed by Liverpool and Broadgreen University Hospitals NHS Trust (reference 2570;

closing date 31st January 2005) and Epsom and St Helier NHS Trust (reference HJUK/ZP/238; closing date 18th March 2005) and caused justifiable offence:

"CFS" patients are said to exhibit "*perpetuating illness behaviour*"; therapists will be required to modify patients' "*predisposing personality style*"; CFS patients have "*complex psychological problems*" and "*experience barriers to understanding*"; there can be "*significant barriers to accepting the changes needed in behaviour, which have to be overcome in therapy*"; therapists can be required to work frequently in an emotive and demanding environment and patients may be "*verbally aggressive*"; "***medical intervention is no longer appropriate***"*; the aim of therapy is to "reduce healthcare usage*"; the service is extended to patients who have mental health problems; the post-holder is expected to "*implement a range of psychological interventions with individuals, couples and families*" and to work with other members of the multi-disciplinary team to "*raise awareness of the approach adopted by the new centres to GPs and other local service providers*".

It seems that the objective was to portray throughout the UK the Wessely School's "CFS profile" and its intended psychiatric management of such patients.

In an article in The Observer in April 2007, AfME's Principal Medical Advisor Professor Pinching wrote: "*There is a 'tool box' available to clinicians to address things that may be interfering with recovery – eg. low self-esteem and depression. Your GP can discuss options available to you, which include cognitive behavioural therapy".*

There is no evidence to show that "low self esteem" either occurs in ME/CFS or interferes with recovery, but there is evidence to show that rates of depression are no higher in ME/CFS than in other chronic medical conditions (Shanks MF and Ho-Yen DO, British Journal of Psychiatry 1995:166:798-801); indeed, the rates of overall psychiatric disorders in ME/CFS are no higher than general community estimates (Hickie I et al. British Journal of Psychiatry 1990:156:534-540).

It is not only Professor Pinching who is closely involved with Action for ME: Professor Michael Sharpe is (or was) an *ad hoc* Medical Advisor to the charity, and on 22nd January 2004 in a debate on ME/CFS in the House of Lords, the Health Minister, Lord Warner, confirmed that Professor Wessely had worked closely with Action for ME, to which the Countess of Mar responded: "*Such is that man's influence that when faced with ME patients, clinicians now collude with each other to ensure that patients receive no investigation, support, treatment, benefits or care – in fact, nothing at all. Patients are effectively abandoned.* ***They have been badly let down by Action for ME****. It is now supporting the Wessely 'management' programme and is, I see, to be actively involved in the development of the new treatment centres"* (Hansard: Lords: 22nd January 2004:656:27:1180).

On what grounds the charity AfME chose to be so closely involved in the PACE trial of GET when its own Preliminary Report of 2001 (published as "Severely Neglected: M.E. in the UK") shows that GET makes 50% of ME patients worse remains to be ascertained.

If it were already known that a drug made 50% of patients worse, would a clinical trial of that drug be permitted to continue, and would people be willing to take part in such a trial?

One PACE Trial participant, herself a mental health professional, has posted her experiences on the internet and has expressed her dismay about the involvement of Action for ME:

"I am most disappointed that AfME has endorsed the PACE Trial.

" I was randomly selected to CBT via the trial, and it was quite apparent that the treatment was flawed from the outset:

a) The therapist misled me by saying he had a 99% recovery rate

b) He could not answer basic questions as to how he measured recovery

c) *I had been told by Dr. X (the doctor I see at the Western General Hospital) that the therapist was a clinical psychologist, only to find out he is only a psychiatric nurse who has then done a diploma in psychotherapy; I received a letter of apology re this only after bringing it to her attention and pointing out the discrepancy via Edinburgh University PACE Trial Website*

d) *After I told the therapist that I was disengaging from the trial, he phoned me 3 times to attend a meeting with him - although it states that you can leave the trial at any time and don`t even have to give a reason. Although the therapist had said the purpose of the meeting was to wish me well for my future, he was very angry and defensive at the meeting due to me disengaging; he obviously had pressure on him to keep his numbers up - but that was no reason to treat me in such a way*

e) *It was quite apparent during the 6 sessions I had with the therapist that he was more interested in his research findings than genuinely helping me.*

"All in all I found the whole experience to be quite damaging, particularly as my expectations were falsely raised and the therapist behaved quite unethically at the last meeting - no doubt due to pressure upon him to get the desired results via his research subjects.

" I think it is incorrect for Action for ME to support and endorse such a trial, and am most disappointed that it does so"
(http://meagenda.wordpress.com/2007/08/01/action-for-me-afme-statement-nhs-collaborative-conference/).

The same person repeated her concerns in a comment posted to The New Statesman website: "*…it was quite obvious to me that the 'therapist' was trying to manipulate the results and had immense pressure put on him to secure specific findings. Due to having studied psychology for 4 years and myself being a psychiatric nurse (as was the therapist), his 'tactics' were very transparent….Although I was extremely ill following a relapse…his concern was only for his research and his behaviour resembled that of a bad car salesman who realised the sale he thought he had secured was slipping from his grasp….Fortunately I have much improved since disengaging from CBT via the PACE Trial which was an extremely negative experience which made my CFS much worse. There is no way any research which relies on self reporting by vulnerable patients that are influenced by unscrupulous 'therapists' with a vested interest in obtaining specific outcomes can be classed as scientific or reliable*" (http://www.newstatesman.com/life-and-society/2008/05/cbt-arthritis-improve#reader-comments).

This person's experience demonstrates how coercive the PACE Trial therapists are prepared to be, and it seems clear from the Manuals that the therapists are specifically trained to be highly coercive.

For AfME to be so intimately involved with the PACE Trial surely ought to be a matter of concern to any of its members who suffer from ME as distinct from chronic fatigue.

The cost of the PACE Trial (and cost-effectiveness)

It is now known that additional funding was granted by the MRC but the cost of the PACE trial to the MRC was originally stated as being £1,921,883.00 and the cost to the NHS as being £1,179,909.00, an initial total of £3,101,792.00 (this figure may exclude the usual 40% add-on which is awarded with Class I grants;) moreover, it is known that this figure has increased substantially.

As noted in Section I above, the cost of the PACE Trial is said by Professor Sharpe to have risen to about £4 million: Co-Cure ACT:RES: 22nd October 2008), a cost that many people regard as scandalous.

The MRC component consisted of research staff costs (£1,097,266.00); Overheads (£504,742.00); Equipment, including Actiwatch Plus activity sensors (the use of which was abandoned because Peter White deemed it too onerous for participants to wear one strapped round an ankle at the end of the trial, but many people

believe it was because there would be no objective evidence of improvement shown by the Actiwatch sensors, a finding that would be inconvenient to the Investigators, therefore no objective data were to be collected), computers and software, heart rate monitors, stop watches, 18 audio machines and 3,150 audiotapes (£36,360.00); Staff Travel (£64,880.00), and Consumables, (£218,635.00); this figure includes Action for ME's consultancy costs of £4,312.00. The NHS component consisted of the cost of therapists.

When recruitment to the trial proved to be such a problem, an additional amount of £702,975.00 was granted by the MRC (MRC PACE Trial extension 2009-2010).

Cost effectiveness of CBT and GET

In terms of the cost-effectiveness of CBT, when NICE was considering the cost-benefit ratio it discovered that there are only two studies that have considered the cost effectiveness of CBT. One was a study by Wessely et al (BJGP 2001:51:15-18). **It showed no benefit from CBT.**

The other was the Severens/Prins et al study (Q J Med 2004:97(3):153-161) that was based on the Prins et al 2001 study of CBT for CFS (Lancet 2001:357:9259:841-847).

Not only did the Prins et al study not include patients with ME/CFS (Prins et al used their own case definition – a modified version of the CDC 1994 definition – which essentially identified patients with idiopathic chronic fatigue, so no conclusions can logically be drawn from it regarding ME/CFS patients), in this single study that NICE could find upon which to rely for its costing of the alleged effectiveness of CBT (Severens et al), the original authors (Prins et al, 2001) admitted flaws which included (i) the self-selection of participants (ii) high drop-out rate for unrecorded reasons (up to 40%), and (iii) a bias between the control group and patients in the treatment arm subjected to CBT.

Furthermore, NICE concluded that this single paper upon which its entire costing analysis relied had under-reported the benefits of CBT because the timescale used by the Dutch authors was insufficient to show long-term benefits (the authors' treatment timescale was only eight months and the follow-up was six months, making only 14 months in total).

NICE therefore decided to "extend" the timescale to fit its own requirements to show long-term benefits of CBT. Since there was no evidence in the Severens et al study, NICE decided to use the 2001 study by Deale, Wessely et al (which was a five-year follow-up of their 1997 paper), from which NICE extrapolated Deale et al's results from data that the authors themselves recognised was corrupted because of multiple further interventions during the study period), and projected those results into the Severens et al study to produce what might have been Severens' results in five years' time.

It should be noted that the two studies used different case definitions and different entry criteria, so NICE's contrived "evidence" is simply conjecture, yet NICE asserts it is the *"best evidence available"*.

To base a national Guideline on such speculation is hardly the standard of excellence that NICE is expected to provide.

In terms of cost-effectiveness of GET, there is no evidence at all. The single study which attempted to demonstrate that GET is more (or indeed less) effective than CBT was unable to show any difference between CBT and GET (McCrone P et al. Psychological Medicine 2004:34:991-999).

For the PACE Trial Investigators to advise that CBT/GET is cost effective for ME/CFS is entirely unproven, yet in the Trial Identifier Peter White confidently states: "*The results of this trial will allow health planners, clinicians and patients to choose treatment on the basis of both efficacy and cost"* (Section 2.5).

The Investigators' Reasons for the PACE Trial

The Trial Identifier states at section 2.5 that the results of this trial will *"provide the first test of pacing against usual medical care"*. Testing this theory hardly requires a multi-million pound trial. Most ME/CFS patients learn from experience that they must **pace** rather than **push** themselves and, as far as ME/CFS is concerned, "*usual medical care*" is non-existent.

Wessely School psychiatrists are disparaging about pacing as a method of self-management. At Section 2.3 the Trial Identifier states:

"*Pacing has been described in the scientific literature as a lifestyle management that allows optimal adaptation to the illness. It has been advocated by exponents of the 'envelope theory' of CFS, which states that a patient has a fixed and finite amount, or envelope, of energy that they must adapt to by managing activity. A non-randomised comparison of adaptive (rather than rehabilitative) CBT, which included adaptive pacing therapy (APT) based on this model, found that this treatment was no more effective than the control condition* (the control condition was primary depression). *A recent systematic review concluded that there was insufficient evidence to recommend adaptive pacing at present*".

It seems that the Trial Investigators may hope to show that pacing is ineffective (especially in returning people to gainful employment) but that CBT and GET are effective in returning people to work.

For Peter White to state that the result of his PACE Trial will allow health planners, clinicians and patients *"to choose treatment on the basis of both efficacy and cost"* is already known to be a non-existent choice, given that the NICE Guideline recommends only CBT and GET and that medical adherence to the NICE Guideline is to become legally enforceable, thus removing any vestige of clinical choice:

"GPs will have to prove they follow NICE Guidelines or face the possibility of suspension, prosecution or the closure of their practice. Baroness Young, chair of the Care Quality Commission, revealed that guidance from NICE would become legally enforceable from 2009, with doctors to face tough annual checks on their compliance. Baroness Young told last week's NICE annual conference that policing clinical guidance was set to be a key part of the CQC's work, and admitted the commission had been handed 'draconian' powers by Ministers" (PULSE: "Threat of legal action if GPs fail to follow NICE"; Nigel Praities; 11th December 2008).

The Trial Identifier also states that the Trial will "*indicate which patient characteristics predict which response to which treatment"* and that it will *"define the essential aspects of effective treatment as a step towards the development of more efficient therapies"* (a possible forecast of the provision of even more psychosocial "Fatigue" Clinics throughout the nation, as both White and Pinching have publicly envisaged in their respective submissions to various Parliamentary committees and inquiries).

In the opinion of many, not a single reason put forward by the Trial Investigators has merit. It is already known that "perpetuating factors" do not, as believed by the Wessely School, include being in receipt of State benefits, having "aberrant illness beliefs", being "deconditioned" or belonging to a self-help organisation.

Many people believe that the MRC PACE Trial was designed and implemented to produce a specific outcome and that this outcome will support the NICE Guideline's recommendation for CBT/GET for "CFS/ME".

Such an outcome would also support the theories and careers of the trial designers and their like-minded colleagues, an outcome that would effectively impose State control of medicine in the UK.

Assumptions made by the Trial Investigators

The Trial outcome is based on assumptions: *"At one year we assume that 60% will improve with CBT, 50% with GET, 25% with APT and 10% with UMC"* (usual medical care, which is not defined and as noted above, is generally accepted to be non-existent for ME/CFS).

The PACE Trial statistician, Dr Tony Johnson, is on record as stating about the trial: *"In designing a clinical trial (of CBT/GET) we have to estimate the number of patients"; "Estimation essentially requires a guess at what the results will be"; "'In guessing what the results may be…"; "'The assumptions we make…"; "'Broadly, we assumed that around 60% of patients in the CBT group would have a 'positive outcome' at one year follow-up…"; "We speculated that…."* (see Appendix I).

Inadequate sub-grouping of trial cohort

There is now an unmistakable recognition that sound biomedical research has strengthened the need for subgrouping of "CFS" and for many years, international experts have been calling for such sub-grouping (http://www.meactionuk.org.uk/Subgroups.htm). A document dated 8th February 2003 was sent to the MRC (Information for the MRC "CFS/ME" Research Advisory Group by Hooper and Williams) which pointed out the need for subgrouping and which quoted Dr Derek Pheby's Discussion Document of February 1999 that was prepared for the Chief Medical Officer's Working Group to consider. In that document, Pheby (then at the Unit of Applied Epidemiology, Frenchay Campus, Bristol) was unequivocal about the need for attention to be given to the existence of subgroups and he quoted from the 1994 Report of the UK National Task Force on CFS / PVFS / ME, which states: ***"Although both the terms "CFS" and "ME" have a range of applications, they do not represent the same populations".***

In his document for the CMO's Working Group Pheby stated:

- *"The National Task Force recommended that five main sets of issues should be addressed, i.e.* ***Clarify the difference between the various chronic fatigue syndromes…*** *areas where in the view of the Task Force research needed to be encouraged included:* ***clear definition of the various chronic fatigue syndromes****"*

- *" CFS is a* ***spectrum*** *of disease"* (quoting Levine), who is emphatic: *"It is clear that CFS is not a single entity"*

- *"Variations in prognosis may be attributable once again to the heterogeneity of the condition,* ***with different subgroups having different prognoses"***

- ***"The heterogeneity of CFS has made it very difficult to interpret research results from different studies which may have been conducted in very dissimilar populations"***

- ***"If progress is to be made, it is necessary to consider…the existence of subgroups within the population of patients with CFS / ME"***

- ***"The increasing knowledge of pathological processes occurring in CFS / ME has led to a belief that it should be possible to define subgroups on the basis of biomarkers and thus to draw a distinction between CFS and ME****".*

Fifteen years later, the Wessely School still refuse to accept the need for subgrouping within the broad "CFS" construct and insist that all states of "medically unexplained fatigue" should be amalgamated. This is contrary to the basic principle of scientific exactitude, yet the MRC, the bastion of scientific exactitude, apparently sees no problem.

In his presentation entitled "NHS Service Implementation Programme for ME – Progress made so far" to the All Party Parliamentary Group on ME on 16th November 2005, Professor Pinching is recorded as having said that he did not accept that evidence existed to justify treating subgroups of ME/CFS patients differently, and Section 3.17 of the Trial Identifier states that there is no intention to perform subgroup analyses of "fatigued" participants.

The PACE Trial is thus a wasted opportunity to advance scientific understanding of "CFS/ME".

Sub-grouping, however, is contrary to the Wessely's School's intention of lumping together all states of "medically unexplained" fatigue, an approach that does not enhance scientific understanding in any way but intentionally obfuscates it.

At the MERUK International Research Conference held on 25th May 2007 at the University of Edinburgh, (which no-one from the Wessely School chose to attend), Professor Nancy Klimas – perhaps the world's most distinguished and respected ME/CFS clinician and researcher – highlighted the need to subgroup patients into at least three main categories: those with autonomic, those with inflammatory and those with endocrine symptoms, which she said would make research *"a data-driven process"*. This is in direct contrast to the Wessely School's seemingly non-scientific *modus operandi* for which they have received many millions of pounds sterling.

Audio and video recordings will be made of participants

The "Invitation to join the PACE trial" leaflet informed participants that: *"We will audio- or video-record the interview when the nurse asks about your emotional and psychological symptoms"*. It is noted that there was to be no recording of patients' physical symptoms. It continues: "*We will also audio- or video-record your treatment sessions"*.

The PACE Trial's emphasis on control is ominous: even the doctors' Standardised Specialist Medical Care ("SSMC") Manual focuses on obtaining **and recording** participants' "admissions" of psycho-emotional aspects of their illness.

It is generally accepted that when people are aware of being recorded/filmed, there is an additional area of subtle pressure being applied to which they will react and which might influence their responses.

Notably, both the CBT (page 26) and GET (page 29) Therapists' Manuals advise therapists that *"If participants are unclear of the reasons, you can remind them that you are doing this for the purposes of supervision, assessment of competence, assessment of therapy differences* ***and other research purposes***", but no explanation is provided.

Could it be for the "research purposes" of the DWP? What do participants understand these "*other research purposes"* to be? Not to inform participants of the precise nature of these "*other research purposes"* does not accord with the research requirement for transparency and would seem to be in breach of the Declaration of Helsinki (see below).

The Wessely School's reason given in the "Invitation to join the PACE Trial" leaflet for such recordings was:

"*We do this to make sure your sessions follow the manual we have written for our study"* and "*We do this to supervise the nurse and to make sure the interview is done properly* ***and the right interpretations are made****"*.

This seems implausible: video recordings of nurses administering potent chemotherapy are not made just so that the nurses delivering the therapy can be supervised.

Are the researchers claiming that an "expert" would check the work of every therapist in every session in every PACE Trial Centre?

Is this deemed necessary because there is concern about the calibre of the therapists recruited and employed for the PACE Trial? It is known from Peter White himself that there were serious difficulties in procuring enough therapists (see Section 2 above).

If so, is delivery of psychotherapy by such people to PACE Trial participants justifiable, especially as the Department of Health is a co-funder of the PACE Trial and its own Research Governance Framework for Health and Social Care states at section 3.1.2:

"*All those involved in research also have a duty to ensure that they and those they manage are appropriately qualified, both by education and experience, for the role they play in relation to any research".*

It seems much more to do with the MRC's concern about indemnity, as recorded in the Minutes of the Joint Trial Steering Group and Data Monitoring and Ethics Committee meeting held on 24th September 2007:

"Action 18: Julia DeCesare to reference MRC GCP (Good Clinical Practice) *Guideline (1998) in section 17, and to add in information on indemnity as provided through NHS R&D* (Research & Development). *Action 19: Robin Buckle to check under the new MRC sponsorship agreement what indemnity the MRC can offer".*

This seems to relate to protection for those running the MRC Trial, not protection for participants. The MRC website states:

> *"MRC will provide indemnity in the case of negligent harm for research conducted through its Units when it is Sponsor* ***and for employees or others acting on behalf of the Council****… The MRC when acting as Sponsor, in some circumstances, may be prepared to offer, on a voluntary basis, an ex-gratia payment in the event of non-negligent harm".*
>
> "*Multi-Centre Research. This is more complicated as, even when the MRC is Sponsor, MRC indemnity should not cover responsibilities of other organisations. If MRC is Sponsor but research takes place at other sites (e.g. NHS hospitals or Universities) then appropriate arrangements should be put in place i.e****. the employers of the researchers at each site accept insurance or indemnity liability for their employees***" (the main sponsor for the PACE Trial is Barts and The London Queen Mary School of Medicine and Dentistry – Full Protocol, page 15).

Severe Adverse Events (SAEs).

The Minutes of the PACE Trial Steering Committee held on 22nd April 2004 record:

"It was noted the (sic) *severe adverse events (e.g. a patient having a stroke) was not necessarily severe adverse reaction (SAR) to treatment. Therefore the procedure for notifying everyone of severe adverse reactions did not apply to all severe adverse events.* ***The definition of SARs in this trial is complex*** *and requires further consideration*".

Given the extensive literature on vascular and inflammatory problems in ME/CFS and the documented increased risk of cardiovascular events in relation to exercise for people with ME/CFS, such a dismissal seems cavalier to say the least.

It is notable that on 27th February 2007 in his annual Report for the PACE Trial to the West Midlands MREC, Professor Peter White informed MREC that of the actual number of participants recruited to that date (222), there had been 21 serious adverse events (which at about 10% is quite a high figure).

Peter White, however, asserted that all were *"definitely unrelated"* to the study treatment. This statement is curious, because of the 21 people who experienced a severe adverse event, it appears that at least 13 chose to continue with the trial.

Peter White informed the West Midlands MREC that 80 participants had completed the trial to that date, and that there had been eight withdrawals from the trial, six of which were self-withdrawals and two were for non-compliance.

If the 8 withdrawals were from the 80 participants who had completed the trial, that is a 10% withdrawal rate up to February 2007.

This hardly accords with the Minutes of the Forward-ME Group of 8th July 2009, which record that Sir Peter Spencer, CEO of Action for ME, said:

"*AfME was associated with PACE and had been pleased with the very low drop-out rates".*

Predictors of Outcome of the PACE Trial

Under *"Predictors of outcome"* in the Trial Identifier, the Principal Investigators state with conviction:

"*Previously found predictors of a negative outcome with treatment include mood disorder, membership of a self-help group, being in receipt of a disability pension, focusing on physical symptoms, and pervasive inactivity".*

No mention is made of the severity of physical illness or of serious and demonstrable organic pathology as predictors of a negative outcome to the Wessely School's own brand of cognitive restructuring.

Outcome measures were discussed at the First Meeting of the Trial Steering Committee held on 22nd April 2004 at St Bartholomew's Hospital, London.

The Minutes record:

"*The outcome measures were discussed.* ***It was noted that there may need to be an adjustment of the threshold needed for entry to ensure improvements were more than trivial***" (emphasis added). This appears to indicate concern that any improvement might be minor and not statistically significant, a result that might be unacceptable to the Investigators.

Outcome measures were discussed again at the Joint Trial Steering Committee and Data Monitoring and Ethics Committee meeting held on 27th September 2004 and the Minutes record:

"*Professor White led discussions on the outcomes, and* ***the Trial Management Group's struggle to find an objective outcome measure as requested by the Trial Steering Committee at their last meeting, particularly as CFS/ME is a subjective condition.***

"Professor Darbyshire led discussion about how to define 'improvement'. The question was asked 'how soon will you know if a participant is getting worse?' to which Professor Chalder responded that previous research has shown that it cannot be determined if people are getting better (sic) *until at least six months after the end of therapy (i.e. a year after therapy has begun). CBT and GET may both make a patient worse before they begin to improve".*

The Minutes do not record an answer being given to the question that was asked, ie. *"how soon will you know if a patient is getting* ***worse****?".*

The Chalder Fatigue Scale as an outcome measure

The outcome measures to be used in the PACE Trial include the Chalder Fatigue Scale (Chalder T, Wessely S et al. Development of a fatigue scale. J Psychsom Res 1993:37:2:147-153).

It is important to note that this does not measure the key symptom of ME/CFS (post-exertional exhaustion and malaise) but only subjective physical and mental "tiredness" or "fatigue".

The Chalder Fatigue Scale has been much used by the Wessely School but its validity has been legitimately questioned.

There are different instruments for scoring symptoms, one being the Likert Scale which has gradations in measurement, for example, patients can rate themselves on a scale of 1 – 5, and can identify if they feel fine (score 1), or quite fatigued (score 3), or if they are exhausted (score 5).

The Chalder Fatigue Scale is different; it is a bimodal scale, which essentially means that it has a two-way answer only -- patients must answer simply "yes" or "no" (ie. they are fatigued or they are not fatigued). It only tells the investigator who is fatigued by the criteria used. It is thus a very crude measurement, because people with ME/CFS cannot give such clear-cut answers and are put at a disadvantage: they are not either "tired" or "not tired" – they vary with different situations.

The Chalder Fatigue Scale makes great claims for the validity of the scale, but it has little, if any, relevance in ME/CFS, especially where subgroups are concerned, because it lacks sensitivity. It is, however, easy to analyse.

The Chalder Fatigue Scale appears incapable of providing an accurate assessment of ME/CFS patients as distinct from fatigued patients. This has been suggested to be because it does not just have a low ceiling for each individual question, but also for the total score.

In simple terms, if a participant already has a maximum score at the start of an intervention (such as GET), then even if the participant feels worse and is actually worse at the end of the intervention, their total score on the Chalder Fatigue scale cannot increase, so there is no evidence that they have been made worse by the intervention. In other words, people cannot be shown to "get worse" on the Chalder Fatigue Scale even if they feel -- and are -- worse.

Stouten analysed commonly used fatigue scales in relation to "CFS", including the Chalder Fatigue Scale, the Checklist Individual Strength and the Krupp fatigue severity. What is clear from this analysis is that the Chalder Fatigue Scale comes out worst and it did not accurately represent the severe physiological exhaustion that is characteristic of (ME)CFS, which should lead to serious questions about its validity and suitability. Abundant extreme scoring and the corresponding inability to discriminate between the various levels of severe fatigue can produce misleading results in several ways (BMC Health Serv Res 2005:5:37).

Furthermore, Goudsmit et al assessed if there were any problems associated with the Chalder Fatigue Scale in relation to (ME)CFS patients and found that the low ceiling of the bimodal model means that this scoring system is not suitable for use in clinical trials (such as the MRC PACE Trial) and that more accurate data may be obtained using a different instrument (Bulletin of the ICFSME: 2009:16:3).

Since it cannot be used to measure the effect of an intervention, Tom Kindlon from Ireland has correctly and repeatedly asked why the 11-item bimodal Chalder Fatigue Scale is being used as a primary outcome measure in these trials (http://www.biomedcentral.com/1741-7015/4/9/comments).

The Chalder Fatigue Scale has been described by an Oxford mathematical physicist as *"a parody of modern scientific measurement"* (personal communication).

To many people, it is incomprehensible how such a method of assessment could be deemed scientific when assessing those with ME/CFS, but the MRC Data Monitoring and Ethics Committee apparently had no problem agreeing to its use as an outcome measure in the PACE Trial.

The bimodal scale itself has been criticised as having limited validity and a potential for misuse (Pittinger DJ. Journal of Career Planning and Employment 1993:54:48-53). It has also been criticised because preference score methods are not bimodal, as they are not a meaningful categorical division of a continuous variable, which argues against its recommendation (Matthews PR. eBMJ 23 August 2004).

Christine Hunter of The Alison Hunter Memorial Foundation raised vital questions about outcome measures that the Trial Investigators have not mentioned:

"What precise measures will be used to assess benefit from these trials? For instance, improved swallowing, less abdominal pain and distension, less vomiting, improved gastric emptying, reduced diarrhoea, weight gain, able to cease nasogastric tube feeding, or headache eased, rolling over in bed unaided? ***"Will the beliefs of the researchers be strongly associated with/reliably predict the trial outcomes?"*** (http://web.archive.org/web/20070831234729/http://ahmf.org/medpolpace.htm).

Many in the international ME/CFS community have little doubt about the answers to those questions, not least because such severely affected patients are excluded from study.

Analyses

There are serious concerns about the analyses of the PACE Trial data; these concerns relate not only to the chosen entry criteria but also to the listed covariates.

Section 12 of the full 226 page Trial Protocol states at 12.3.2: *"Secondary analyses of efficacy – The secondary continuous outcomes will be analysed by repeated measures analysis of variance using a linear mixed model with AR(1) covariance structure, and including centre, depressive disorder, CDC* ***and London criteria*** *and baseline values as covariates".*

The Oxford criteria

As noted above, the entry criteria for the PACE Trial are the psychiatrists' own criteria (the 1991 Oxford criteria).

The Oxford criteria have never been adopted internationally. There is no consensus about them; they are used only in Britain and only by the Wessely School. As noted above, they lack diagnostic specificity, have been shown to have no predictive validity, and to select a widely heterogeneous patient population. It is virtually unheard of for studies to use criteria that have been superseded (as mentioned above, Michael Sharpe himself – who was lead author of the Oxford criteria -- stated in 1997 that the Oxford criteria *"have been superseded by international consensus"*.

The Oxford criteria stipulate that people with *"organic brain diseases"* are to be excluded. ME is a classified neurological disorder, therefore the correct application of the entry criteria would result in the screening out of people with ME from the PACE Trial.

There can be no credible doubt that the Oxford case definition excludes those with neurological disorders and as noted above, this was confirmed in 1991 by psychiatrist Anthony David (colleague of Simon Wessely and co-author of the Oxford criteria): ***"British investigators have put forward an alternative, less strict, operational definition which is essentially chronic fatigue in the absence of neurological signs (but) with psychiatric symptoms as common associated features"*** (Postviral syndrome and psychiatry. AS David. British Medical Bulletin 1991:47:4:966-988).

Clearly, therefore, the Oxford criteria do not identify patients with ME, yet the Wessely School and the MRC insist otherwise.

On 16th June 2005, Sarah Perkins, Programme Manager, MRC Neurosciences and Mental Health Board, confirmed: "*The main entry criteria for the PACE Trial are the Oxford criteria…the exclusion criteria of 'proven organic brain disease' will be used to exclude neurological conditions of established anatomical pathology such as Parkinson's disease and multiple sclerosis.* ***It will not be used to exclude patients with a diagnosis of ME****".*

Given that the Oxford criteria expressly exclude those with organic brain disease and that the WHO classifies ME as a neurological organic disease under Disorders of Brain, Sarah Perkins was asked why the MRC was adopting special pleading in relation to ME, and on what scientific evidence-base the MRC was relying to enable it to disregard the ICD-10 classification that had been approved by the World Health Assembly.

Furthermore, given that the Wessely School psychiatrists demand 100% proof of organic pathoaetiology for ME before they will "allow" it to be accepted as a "real" organic disease as distinct from a mental disorder, she was also asked why the MRC does not equally require a similar standard of proof from the Wessely School that ME is indeed a mental disorder as they assert.

She did not reply.

Despite their insistence that they are studying people with "CFS/ME", the Wessely School do not accept that ME is a neurological disorder, so it is unlikely that an assessment which would identify the relevant signs and markers of ME would be carried out on PACE Trial subjects.

Without such an assessment it is not possible to be confident that people with ME have been screened out, so the possibility remains that some participants recruited to the PACE behavioural research trial actually have ME, which may mean that at least some participants have a disorder that contra-indicates the interventions concerned.

If there is no strict adherence to the entry criteria, then the results will be flawed from the outset -- either the criteria are adhered to, or the results will be flawed: there is no other scientifically credible interpretation.

<u>The CDC criteria</u>

As noted above, one of the PACE Trial Principal Investigators (Michael Sharpe) was a co-author of the 1994 CDC (Fukuda) criteria and, as a member of the International CFS Study Group who advised the authors, Simon Wessely was also involved, and they successfully incorporated elements of the Wessely School's model of "CFS" into the CDC 1994 definition.

The 1994 CDC criteria do not stipulate the presence of the cardinal feature of ME, which is post-exertional malaise (it is optional) As a result, the 1994 CDC definition does not identify people with ME as distinct from those with psychiatric fatigue because it includes people with psychiatric disorders; moreover, the 1994 CDC definition dropped all physical signs, but physical signs are always present in ME (see Section 2 above).

<u>The "London" criteria</u>

In apparent response to public disquiet about the use of the Oxford criteria for entry, it was confirmed by the MRC that there was to be an additional "secondary analysis" of the data using the "London criteria", but there is no mention of any "secondary analysis" using the "London criteria" in the original Trial Identifier.

In her communication of 16th June 2005 (referred to above), Sarah Perkins from the MRC stated: "*The investigators have also chosen to ascertain which other definitions participants fulfil. The 'London criteria' for ME are described in the National Task Force report (1994). These criteria are based on the original description of ME by Dr Melvin Ramsay (1978)…They have validity for some patients and clinicians but have not to our knowledge been used in any major research studies. I should emphasise that the London criteria will not be used as an inclusion criteria* (sic) *but will be used as predictors of response to treatment"*.

It is a straightforward fact that if those with a classified neurological disorder are excluded from the outset by virtue of the Oxford entry criteria, no amount of "secondary analysis" will reveal those with a classified neurological disorder.

Professor Peter White informed the Joint Trial Steering Committee and Data Monitoring and Ethics Committee on 27th September 2004 that the London criteria have not previously been used in research.

That is unsurprising, since the "London criteria" do not formally exist (although the PI's own version is provided on page 188 of the Full Protocol).

White was incorrect, because Jason et al used one of the several versions of the proposed (but unpublished) "London criteria" in the paper "Variability in Diagnostic Criteria for Chronic Fatigue Syndrome May Result in Substantial Differences in Patterns of Symptoms and Disability" (Eval Health Prof 2003:26(1):3-22).

The reference for the "London criteria" given by the PACE Trial Investigators (reference number 31 in the full Protocol and reference number 40 in the abridged Protocol) cites in both versions: "*The London criteria, quoted in The National Task Force Report on Chronic Fatigue Syndrome (CFS), Post Viral Fatigue Syndrome (PVFS) and Myalgic Encephalomyelitis (ME). Bristol. Westcare; 1994"*.

That is misleading, because The National Task Force Report states on page 89: "*Recently IFMEA* (International Federation of ME Associations), *Action for ME and the ME Association have proposed 'London criteria' for ME/PVFS".* Thus the "London criteria" were merely **proposed** criteria and were never ratified.

Confusingly, the Chief Medical Officer's Working Group Report on CFS (2002) refers on page 76 in its Appendix II (Existing Diagnostic Criteria) to the "London criteria" and explains that they were "*Derived from Dowsett & Ramsay"*. However, the Dowsett and Ramsay paper in question does not mention the term "London criteria" (Myalgic encephalomyelitis – a persistent enteroviral infection? Postgrad Med J 1990:66:526-530). Dowsett and Ramsay simply said they *"adopted the following clinical criteria"* for the selection of patients for that one study, which does not constitute "existing diagnostic criteria".

Moreover, the misleading reference for the "London criteria" which appears in the CMO's Working Group Report (the alleged Dowsett and Ramsay definition) is not the reference given by the PACE Trial Investigators, which is the National Task Force Report, which simply refers to the **proposed** "London criteria".

The NICE Clinical Guideline on CFS/ME (CG53) Draft for Consultation of September 2006 also referred to the "London criteria" as though they actually exist ("Dowsett ME", reference number 12 and Perrin et al, reference number 199 – see below), whilst the final version of the Guideline briefly mentioned "Dowsett ME" on page 144 but did not include the Perrin et al paper.

The issue of case definition to be used by the MRC for "secondary analysis" is of cardinal importance, yet the provenance of the "London criteria" has not been established and they have never been published in any medical journal. 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); they have never been operationalised or validated and despite there being much internet traffic about the alleged authorship, it remains uncertain who the authors are.

Since the "London criteria" have never been published, they have no authors as far as the real world is concerned.

Notwithstanding, claims were made on the internet by one of the purported authors of the proposed "London criteria" that they had been operationalised, and that five published studies had used them. Those studies were alleged to be:

(i) Costa, Tannock and Brostoff (Q J Med 1995:88:767-773), which makes no mention of the "London criteria" but does cite as reference 14 *"Criteria for a diagnosis of ME…based on the criteria suggested by WRC Weir in Postviral Fatigue Syndrome by Jenkins and Mowbray, pp 248-249"*. The Jenkins and Mowbray textbook sets out Dr William Weir's own modification of the Holmes et al 1988 criteria and is virtually identical to the subsequently proposed "London criteria" set out in the National Task Force Report

(ii) Raymond Perrin (an osteopath) claimed in a 1998 study for his PhD that he had used both the 1994 CDC criteria and the "London criteria" (J Med Eng Technol 1998:22:1-13). When contacted, he expressed surprise because he had been led to believe that the "London criteria" had been published and validated. He confirmed that he had accepted assurance from someone connected with Action for ME that the "London criteria" had been published, an assertion that originated from the same person who made other claims for the "London criteria". Mr Perrin confirmed that he would have to amend his thesis

(iii) Paul L et al (European Journal of Neurology 1999:6:63-69), which did not mention the "London criteria"; the authors state: *"The patients… fulfilled established criteria for CFS (Fukuda et al, 1994)"*

(iv) Whiting et al (The York Systematic Review: JAMA 2001:286:11:1360-1368), which did not mention the "London criteria"

(v) McCue, Scholey and Wesnes (Proceedings of the British Psychological Society, 12th January 1999); this was a poster presentation at a BPS Conference, which does state that the 20 patient satisfied the "London criteria", although the criteria were not defined in the abstract. Poster presentations are not published studies. Direct personal contact was made with Professor Andrew Scholey, who confirmed that his work on ME had not been published.

The key point about the intended use of the "London criteria" by the PACE Trial Investigators is that they are not on PubMed and are not available for scrutiny. How is it possible for the MRC to claim scientific validity by using criteria that do not formally exist and which cannot be accessed for comparison? Is this the "high standard of excellence" claimed by the MRC?

The PIs specifically predict in the Protocol that those who satisfy the "London criteria" will do less well, but how is it possible to enter into a statistical model a covariate based on a case definition that has never been published and does not formally exist?

This appears to amount to significant internal inconsistency.

Of importance is what the PIs state about their "London criteria for ME" on pages 188 - 190 of the Full Protocol (note that whilst some patients do experience tinnitus, it is not a cardinal symptom of ME):

"Criteria 1 to 4 must be met for a diagnosis of ME to be made.

1. Exercise-induced fatigue precipitated by trivially small exertion (physical or mental)
*2. Impairment of short-term memory <u>and</u> loss of powers of concentration, usually coupled with other [neurological or psychological] disturbances…[**NB These symptoms should be asked for as symptoms…These symptoms in (a – e) should be recorded, <u>but are not necessary to make the diagnosis</u>]:***

a) emotional lability….b)…difficulty finding the right word c) disturbed sleep patterns d) … a feeling of imbalance e) tinnitus [ringing in the ears]
3. Fluctuation of symptoms usually precipitated by either physical or mental exercise. ***[NB The usual precipitation by 'physical or mental exercise' should be recorded but is not necessary to meet criteria]***
4. These symptoms should have been present for at least 6 months and should be ongoing
5. There is no primary depressive illness or anxiety disorder/neurosis. ***[NB This means that if any depressive or anxiety disorder is present, the London criteria are not met]".***

The criteria were to be judged by the Research Nurse, who was advised that psychiatric exclusions are schizophrenia, bipolar illness, substance misuse, eating disorder, and proven organic brain disease; however, the RN was specifically advised that *"Other psychiatric disorders (including depressive illness, anxiety disorders, and hyperventilation syndrome) are not reasons for exclusion".*

Criterion 1 and criterion 3 appear to be mutually exclusive. Furthermore, if criteria a-e are unnecessary for a diagnosis of ME by the PI's London criteria, all that is left is the Oxford criteria with no requirement for neurological symptoms (but with the absence of depression or anxiety as assessed by the Research Nurse, which does not exclude assessor bias). Dowsett & Ramsay stipulated that neurological disturbance **must** be present, yet the PIs state in their criterion 2 that neurological disturbances are not necessary to make a diagnosis.

What is left is an entirely inadequate description of the neurological disease ME and does not further the delineation of scientifically meaningful subgroups.

In the 2005 empirical definition by William Reeves et al from the US, CFS is described demeaningly as "*chronic un-wellness"*(BMC Med 2005:3:19), about which Peter White stated in the Trial Identifier at Section 3.6: *"The more narrowly defined CDC criteria* (ie. the 1994 Fukuda criteria) *are about to be…superseded by an empirically derived definition [and] PDW is a member of the CDC led group"*, thus endorsing the term "*chronic un-wellness"* as an acceptable description of ME/CFS.

This is all the more disturbing given that on 31st March 2003 the West Midlands Multi-centre Research Ethics Committee wrote to Peter White about ***"THE FINAL DOCUMENTS AND ARRANAGEMENTS APPROVED BY THE MREC"***, saying: "*The documents that have now been approved are as follows"*; item 8 on that list is a date-stamped copy of "*Dr Melvin Ramsay's description of myalgic encephalomyelitis"* (marked "*RECEIVED 21 MAR 2003"*). A scanned copy of the Ramsay definition that was approved by the MREC is attached as Appendix III to this Report.

Two years later, however, by letter dated 2nd February 2005 the West Midlands MREC acknowledged Peter White's letter to them received on 7th January 2005, saying: "*It is noted that this is a modification of an amendment previously rejected by the Committee".* The list of approved documents no longer contains Dr Ramsay's definition of ME but does list "*London criteria for ME".*

It is beyond doubt that symptoms necessary to comply with Ramsay-defined ME do not feature in the PACE Trial and are not included in the version of the "London" criteria as set out on page 188 of the Full Protocol. It appears that the "London" criteria were substituted for the Ramsay definition and that the PACE Trial version of the "London" criteria does not require the presence of neurological disturbance (which is a cardinal requirement in Ramsay's definition).

In the ME Association's magazine "ME Essential", October 2004, the three PACE Trial Principal Investigators responded to the criticisms of the trial that had been published in "ME Essential" in July 2004; the PIs stated: "*"We note the ME Essential article supports the use of the Oxford criteria and not using the Canadian criteria for CFS/ME, as the former are most inclusive and will allow us to see if different subgroups (for example those who meet the criteria for ME) respond differently to the treatments…We welcome the endorsement of the inclusion of the London criteria for ME as a possible predictor of response to treatment".*

The PIs' statement is interesting because there is a significant difference between subgrouping according to symptoms and stratifying according to different case definitions – it would be impossible to subgroup on the basis of case definition because the categories are not discrete (ie. there is too much overlap).

The PIs' statement is even more interesting in the light of the documented chronology:

- in September 2002 Peter White submitted the first application to the West Midlands MREC, date stamped 12th September 2002. The Oxford criteria are mentioned in the application

- in March 2003 Peter White submitted a revised application date stamped 21st March 2003, which included the Oxford criteria, Dr Ramsay's description of ME, the 1994 CDC Fukuda criteria, but <u>not</u> the London criteria

- the Trial Identifier was also included in that bundle and it states: "*We will also examine whether CDC or 'ME' criteria define response"*

- it can thus be said that from (at latest) 21st March 2003 Peter White intended to use Ramsay's definition of ME, as demonstrated by the written approval of West Midlands MREC

- the first mention of the London criteria in the MREC literature appears two months later: "*Substantial Amendment 2.1, 22.10.2004:* ***We have made some minor changes to the protocol…to ensure we are measuring predictors…that patient organisations believe are important (London criteria for myalgic encephalomyelitis)***" (emphasis added)

- thus sometime between March 2003 and October 2004 the PIs decided to abandon the Ramsay definition of ME and to adopt a version of the "London" criteria following insistence from someone connected with AfME

- in contrast to the Ramsay definition, AfME's attenuated version of the proposed "London" criteria set out in the Full Protocol does not require the presence of any neurological disturbance for a diagnosis of ME, which would lessen the distinction between true ME and "medically unexplained fatigue" (a somatisation disorder).

<u>The intention to use the outcome of the PACE Trial to inform a revision of the NICE Guideline</u>

Referring to a future revision of the NICE Guideline (CG53), the PACE Participants' Newsletter Issue 3 of December 2008 robustly forecast that the outcome of the PACE Trial *"will enrich the guidelines in 2009"*. This is curious, given that the same Newsletter states on the same page: *"We will be very busy analysing the main results of the trial in the spring of 2010"*, so it is unclear by what transparent process the unpublished PACE Trial results will inform the forthcoming revision of CG53 that the PACE Participants' Newsletter says is to take place one year before the PACE Trial results are to be published.

The pronouncement may, however, be taken to support the belief of the ME/CFS community that the outcome of the PACE Trial is – as was the outcome of the NICE Guideline on "CFS/ME" – a foregone conclusion.

For the avoidance of doubt, the PACE Participants' Newsletter was incorrect. A Written Answer to a Parliamentary Question tabled by the Countess of Mar states: *"The National Institute for Health and Clinical Excellence will consider in August 2010 whether there is a need to review its clinical guideline on Chronic fatigue syndrome / myalgic encephalomyelitis"* (Hansard: Lords: 5th May 2009).

Undue influence on the PACE Trial outcome?

As mentioned above, the PACE Trial staff produce participants' newsletters. One reason why a research team might include participants' newsletters in their study design is to encourage participants to remain within the project. This might be especially useful when long-term follow-up is an aspect of a trial. Newsletters aimed at offering general information to trial participants are not unknown (Blanton S et al. Physical Therapy 2006:86:11:1520-1533) but the PACE Trial Newsletters go further than simply providing general information.

From the first issue (June 2006), PACE Trial participants were urged to send "*any feedback on any aspect of the study*".

The same issue says: "*We have already received some informal feedback on the experience of participating in the study. Comments so far received have included: 'I really think it is good to be part of something that will make a difference to so many people'. ' We need this research to know the best treatments'. 'The staff were so professional that I felt well taken care of' ".* It also says: "*Our website is intended to keep all our participants up to date on the trial. We would love to hear what you think of it".*

The second Participants' Newsletter (March 2007) says: "*In our last newsletter we asked for feedback and for contributions from participants and we can happily report that we have received both. Many thanks to those of you who contacted us…and a special thanks to G.T.Buchan who sent us the poems printed overleaf.* ***Any similar contribution from participants who are receiving any of the trial treatments will be gratefully received****".* The poems were full of praise for the PACE Trial.

Issue 3 of the Participants' Newsletter (December 2008) said: "*We would love to hear more of your feedback and see more contributions to this newsletter from participants of PACE".* The same issue contained six glowing reports of the trial from participants (eg. ***"The therapy was excellent"; "(The treatment) is now a way of life for me"; "(The therapist) is very helpful and gives me very useful advice and also motivates me"; "Found (the treatment) extremely useful"****),* together with "***A doctor's feedback***" from the doctor of a patient attending the Bristol PACE Trial centre, which says:*"****I just wanted to feed back to you positive changes I have seen in (patient X) since participating in your trial. I know the therapy is recommended…for CFS, but this is the first time I have seen such a well thought out programme put into practice…I would strongly support any extension of the trial, which clearly has the potential to transform the lives of many people suffering with this debilitating disease. Congratulations to yourself and your colleagues in such a successful programme****".*

No adverse comments were published in the Participants' Newsletters.

Providing participants with adequate information is obligatory, but exposing participants or potential participants to selected opinions of other participants (and of a doctor) is uncalled for in an on-going trial.

Inviting and publishing letters of praise for a clinical trial that is not yet complete might be deemed unethical and might even invalidate the whole trial.

If, for example, those people who had written in such glowing terms at the start of the interventions subsequently knew they had not in fact improved at the end of the trial, they would be unlikely to admit so in the subjective questionnaire which is intended to inform the outcome, as the published letters would surely influence those participants' subsequent answers to their outcome questionnaires.

For trial participants to be praising the trial <u>during a research project</u> ought to invalidate their own data.

Giving participants information that could influence the data they themselves provide – by exposing them to the selected opinion of other participants – might be viewed as publishing selective data from the trial

before it was completed. If some participants' subjective observations are part of the data for the trial, then that data might be deemed not to meet the requirements of proper MRC research practice.

By providing such glowing praise about the PACE Trial to other participants indirectly but improperly makes it less likely that the people who wrote it would dare to disagree with what appears to be a substantial weight of opinion, especially as some of it came from a doctor.

This tactic could be construed at best as unduly influencing participants (because the PACE Newsletters all bear the logos of the MRC, the Scottish Chief Scientist's Office, the Department of Health and the Department for Work and Pensions, which imbues the Newsletters with kudos and authority, suggesting that the contents are reliable and of the highest standard) and at worst as a political strategy that has no place in medical research.

The point of an RCT is to try to factor out any uncontrollable influence that may affect the results, but in this case the PACE Trial Investigators have actually brought in an influence for which they cannot control. That is bad science.

The study designers believe that "CFS/ME" is a psychosocial disorder that is susceptible to positive thinking, and it seems that they have used psychological cajoling strategies such as "let's all get better with the PACE Trial", which may have been designed to make recovery seem trendy and socially attractive.

Researchers have a responsibility not to harm participants, but if a PACE Trial participant found that s/he was not improving, on reading such favourable comments from other participants, they might feel that their lack of improvement was their own failure, especially as participants in the CBT and GET arms of the Trial are informed throughout their own Manuals that – without qualification – recovery is possible with CBT/GET.

When participants are recruited from a patient population known to have suffered stigma and marginalisation, such tactics are not something that responsible researchers would want to risk without ethical approval. Was ethical approval for this obvious strategy sought or approved?

The MRC's Public Relations (PR) Strategy

The question to be asked is: what kind of clinical trial needs a PR (public relations) strategy?

The Minutes of the Trial Steering Committee meeting held on 22nd April 2004 record:

"*The need for active public relations strategy that involved the Principal Investigators, the Trial Management Group, MRC and Action for ME was strongly endorsed. The Trial Steering Committee suggested that the PR (public relations) policy for potential and actual participants was particularly important.* ***It was also agreed that there needed to be a specific working group to plan the public relation strategy and that this would have the following elements: Positive public education and information about the trial (and) the correction of disinformation being circulated about the trial. It was agreed that the Principal Investigators would meet with the MRC and Action for ME to develop a media strategy".***

This documented need for such a PR strategy indicates that those involved with the PACE Trial were fully aware of the level of public disquiet about the Trial.

Of particular note is the letter dated 15th September 2004 from Rhiannon Powell of Chandler Chicco Agency (a PR and lobbying firm) to Mansel Aylward (then Chief Medical Advisor to the Department for Work and

Pensions) and copied to the PACE team, **which specifically mentions lobbying Members of Parliament about the PACE Trial.**

Rhiannon Powell's letter also refers to the Government's Pathways to Work programme; a *"1200% increase back to work"* is mentioned in her letter (*"one delegate was keen to know the number of people a 1200% increase back to work equates to").* It is perhaps noteworthy that Sir Hugh Sykes (brother of Richard Sykes PhD whose work on "Conceptual Issues in Somatoform and Similar Disorders" is referred to in Section 1 above) is a non-executive Director of A4e (Action for Employment), the largest European provider of Welfare to Work programmes and author of "Welfare to Work – The New Deal: Maximising the Benefits" (with grateful acknowledgement to http://meagenda.wordpress.com).

Rhiannon Powell's letter goes on to say that among Chandler Chicco's forthcoming actions was *"the possibility of us contacting someone involved in raising awareness for the issue for people with chronic fatigue* (sic)".

Professor Aylward's annotated reply suggests that she should contact Chris Clark of *"Action for CFS/ME"*.

Action for ME, of course, is a Government-funded charity, which seems to demonstrate the impregnable circularity of the Wessely School's *modus operandi*.

Minutes of the Joint Trial Steering Committee and Data Monitoring and Ethics Committee meeting held on 27th September 2004 record that Professor Dieppe (Chair of the Data Monitoring and Ethics Committee):

"expressed anxiety that recruitment might be impeded by the anti-PACE/FINE lobbyists. Professor Sharpe and Professor White stated that lobby groups had not previously affected recruitment in trials of GET, which is the most controversial of the therapies to be tested".

The same Minutes record:

"*The question was asked as to how to deal with any emails or hateful correspondence received. It was agreed that these should not be directly responded to, but should be retained as evidence for the future should it be needed. ACTION 45: Any lobbyist mail to be forwarded to Julia DeCesare for storage".*

The retaining as "*evidence*"of <u>any</u> "*lobbyist mail*" as "*evidence for the future*" seems sinister, especially when such "*lobbyist*" mail may be the desperate pleadings of sick people seeking appropriate investigations and care.

These Minutes once again seem to show that both Professors Sharpe and White were fully aware of the controversial nature of the MRC PACE Trial, particularly of the GET arm of the Trial.

By their specifically acknowledging that the GET arm is "particularly" controversial, they indicated that they accept that the CBT arm of the Trial is also controversial, so their attempts in the media to allay public concern by asserting that media reports about the PACE Trial are "*inaccurate"* may seem duplicitous.

The Wessely School seem to lose no opportunity to invoke the concept of "controversy" when discussing ME/CFS.

They seem to use this as a tactic of disparagement – they imply that <u>doctors</u> know that ME/CFS (or "CFS/ME") is a somatoform disorder, but <u>patients</u> cause "controversy" because they will not accept that "doctor knows best".

The MRC's denial of any PR strategy in relation to the PACE Trial

Having seen the MRC Minutes quoted above, a request was made to the MRC asking for details of the PACE Trial PR policy, to which request the MRC responded by saying that there was no PR policy concerning the PACE Trial.

This was remarkable, because there is a record of the MRC's concern about the ME Association's campaign against the PACE Trial, as confirmed in the letter of 24th August 2004 sent by Peter White to members of the PACE team, which demonstrates their intention to counter the ME Association's campaign to stop the PACE Trial.

There is also clear evidence of the determination of Peter White and Professor Colin Blakemore (then Chief Executive of the MRC) quickly to counter any negative publicity and to put their own spin on the story. On 11th May 2004 Peter White wrote to members of the PACE Trial team saying:

"*Dear colleagues, Yesterday The Independent carried an article, which criticized the PACE and FINE trials. This article and three letters in response are copied below for your information. I am pleased to say that I understand that the Independent will publish all three letters this Thursday*".

This appeared to indicate that White had secured a promise that a letter that was jointly signed by himself, Michael Sharpe, Trudie Chalder and Alison Wearden was indeed to be published, as was a similar letter from Professor Colin Blakemore; the letter from Chris Clark of Action for ME, however, was not published.

After a further exchange of letters with the MRC about its denial of a PR policy for the PACE Trial, a complaint was made to the Information Commissioner's Office (ICO).

The complaint was duly investigated and on 14th February 2008 the ICO's decision was despatched. From the ICO's investigation, it is clear that there was a PR policy for the PACE Trial, and that the Trial Steering Committee did plan a PR policy as described in the Minutes, and the meeting referred to in those minutes did take place in May 2004, but it seems that there was no "formal" note of that meeting.

The MRC was compelled to confirm to the ICO that there was initially a very serious intention to develop a PR strategy for the PACE Trial.

As noted above, the ICO's decision letter notes: "*The MRC has expressed its concern about how you came to be in possession of the first Minutes of the TSC*". It seems that communications at the MRC may not be of the highest order.

Notwithstanding the content of those documents, the ICO said it was satisfied that, despite the initial intention, there was no "formal" managed PR strategy in place at the MRC for the PACE Trial.

Despite such clarification from the ICO, many in the ME/CFS community remain less than convinced.

Confidentiality of PACE participants' data

PACE Trial participants were promised that their data would be secure.

The "Invitation to join the PACE trial" leaflet assured participants of confidentiality:

"*The data and recordings we collect will be securely stored for 20 years after the end of the trial, for your protection and to follow good clinical practice (GCP). The same applies to other records gathered for our study, including your medical notes and the database holding the collected data from the trial. Your name, address and telephone number will be on*

only one database. This will be held securely at St Bartholomew's Hospital, in London, and it will be used only to monitor recruitment. You will not be named in any published study results from our study".

However, the leaflet also said: "*occasionally, other researchers will need to see your notes so that they can audit the quality of our work. An audit might be run by one of the universities helping with our study or hospital regulatory authorities, or by one of the organisations funding our study".*

As already noted, funders are the Medical Research Council; the Scottish Chief Scientist's Office; the Department of Health and the Department for Work and Pensions.

The leaflet says that participants are to be questioned about how "CFS/ME" has affected them financially, which for patients on DWP State benefits may be a cause for concern, especially as the DWP has the right to access this data and it is widely believed that the intention is to remove as many people as possible from State benefits.

If the PACE trial therapists and Investigators deem a participant "recovered" enough to resume work, then might that participant quickly discover that the DWP has stopped paying benefit? The MRC PACE Trial has been described as a "Trojan horse" for the DWP.

Was it made clear to all participants (some of whom may be cognitively impaired) that, as co-funder of the PACE Trial, the DWP would have access to their personal clinical notes? Would participants have been willing to sign up for the PACE Trial if so?

Furthermore, if State benefits are withdrawn from PACE Trial participants, this would serve as "proof" that the Wessely School's programme of CBT/GET is effective and -- to the detriment of genuine ME/CFS patients – the Wessely School's psychosocial interventions will be further rolled out across the nation, as seems to be intended.

When the PACE Trial had been running for two years, the Participants' newsletter (Issue 1, June 2006) reaffirmed that the trial data was safe:

"*The information is being entered onto a large and secure database, designed and maintained by an independent clinical trial unit at King's College, London".*

This seems to conflict with the "Invitation to join the PACE Trial" leaflet (see above), which states that the data will be held securely at St Bartholomew's Hospital.

Concerning confidentiality, participants who asked: *"Will you keep my details confidential?"* were to be told:

"*Yes. All your details and all recordings will be kept strictly confidential* ***and held in a locked filing cabinet*** *or on a secure computer"* (SSMC Participant Information Sheet for PACE Trial).

<u>Failure of PACE Trial Investigators to ensure confidentiality (theft of data)</u>

Assurance of confidentiality may, however, be a meaningless promise. It was in 2005 (ie. during the life of the PACE trial) that one of the PACE Trial Principal Investigators, Professor Michael Sharpe, inadvertently leaked a computer file containing a confidential list of over 70 patients' names and addresses which he sent to a member of the public, who unknowingly forwarded the information to other people.

Most of the named patients, some of whom live in sheltered accommodation, can be – and have been -- identified.

Some of the confidential information consisted of personal statements made by patients to a number of high-profile Professors and Consultants involved in the Scottish Neurological Symptoms Study, including Professor Richard Warlow; Dr Richard Davenport; Dr Colin Mumford; Dr Christian Lueck (now an Assistant Professor in Australia); Dr Cathie Sudlow; Dr Roger Cull and Dr Adam Zeman.

The large-scale study from which the confidential data was leaked was co-authored by Professor Michael Sharpe and Dr Alan Carson and was looking at the prevalence of medically unexplained symptoms (MUS) in new patients attending Scottish Neurology clinics, particularly at: *"illness-related beliefs and behaviours, what predicts poor outcome, and how these patients are currently managed".*

The study stated that patients with MUS place a *"substantial burden on both the NHS and the economy generally"*. It concluded that *"nearly a third of patients attending Scottish Neurology clinics have medically unexplained symptoms"* which, given the well-published beliefs of Professor Sharpe, is an unsurprising conclusion.

Sharpe (who, with other members of the Wessely School, works for the medical and permanent health insurance industry) has intransigent beliefs about people with MUS, in which he includes patients with ME/CFS.

This serious breach of confidentiality by Professor Sharpe was reported by Ian Johnston in The Scotsman on 19th August 2005. The University of Edinburgh promised to launch an investigation; a spokeswoman said at the time that Professor Sharpe had been made aware of the situation but was on holiday.

It seems that he was not censured in any way.

This event makes clear that there cannot be any guarantee of confidentiality for PACE Trial participants, and indeed **there has already been a serious loss of PACE Trial confidential data.**

On 31st March 2006 Peter White wrote to the West Midlands Multi-centre Research Ethics Committee to inform them of the theft of a digital audio recording (DAR) of GET sessions from Centre 03 (which is King's College, ie. Trudie Chalder's Centre). This confidential information was stolen from an unlocked drawer in the therapists' office. Peter White informed West Midland MREC that: *"**There are no lockable cabinets in any of the therapists' rooms so the drawer was not locked**"* (*cf* SSMC Participant Information Sheet). His letter continued:

"*The burglary was reported to Southwark police on the day that it happened, which was Wednesday 22nd March 2006. The crime number is 3010018-06. The therapist was away on leave 22nd-24th March and therefore the DAR was not found to be missing until Monday 27th March 2006*". It was only <u>after</u> the theft that Professor Trudie Chalder sought advice on how to secure the data properly.

The letter also said: "*The Principal Investigator for this centre, Professor Trudie Chalder, is awaiting advice from the Trust R&D as to whether the affected participants should be made aware of the theft".*

The same letter stated that recordings were being downloaded to CD only on a monthly basis, a working methodology that is not compatible with the promises of confidentiality set out in the "Invitation to join the PACE trial" leaflet.

The letter carries a handwritten annotation dated 13th April 2006: "*Noted. Sad! No action needed".*

It seems that the patients involved were not warned that confidential information about them had been stolen.

Conflicts of interest of those involved with the PACE Trial

In an editorial in The British Journal of Psychiatry (2008:193:91-92), Mario Maj, Professor of Psychiatry at the University of Naples and editor of "Somatoform Disorders" (John Wiley & Sons, 2005, to which as mentioned in Section 1 above, Professors Simon Wessely and Michael Sharpe contributed) drew attention to what he referred to as a major problem in psychiatry:

*"Conflicts of interest occur when doctors are unduly influenced by a secondary interest…The secondary interests that may unduly influence doctors' actions include: financial gain…career advancement or visibility in the media…**the allegiance to a school of thought; and political commitment".***

Maj noted the possible conflict of interest between a psychiatrist's allegiance to a given school of thought and the primary interest represented by the progress of science. He said:

"Along with the fact that the proponents of some specific psychotherapies may be less interested in the scientific validation of their techniques, this allegiance effect may bias the evidence concerning the relative efficacy of the various psychotherapies" and he noted the possible conflict between the secondary interest *"represented by a psychiatrist's political commitment and the primary interest represented by the patients' welfare".*

Maj continued: ***"It has been rightly pointed out that there are now in our field 'special interest groups', consisting of prominent opinion leaders with significant financial conflicts of interest who exercise a powerful impact on the field in their various capacities (e.g. as editors or referees of scientific journals, or as contributors to treatment guidelines…(who have) significant non-financial conflicts of interest arising from their strong political commitment. They may exercise an equally powerful impact on our field acting, for instance, as contributors to mental health policy guidelines or consultants to governments. Moreover, when acting as referees for scientific journals or evaluating research projects submitted to public agencies, they may…unfairly favour colleagues who share their political credo".***

There are many who believe that this applies to the Wessely School.

The Association of Medical Research Charities "Guidelines on Good Research Practice" states: ***"Researchers should declare and manage any real or potential conflicts of interest, both financial and professional.*** *These might include:* ***Where researchers have an existing or potential financial interest in the outcome of the research****: Where the researcher's personal or professional gain arising from the research may be more than might be usual for research".* Unfortunately, these Guidelines are not binding upon the PACE Trial Investigators.

The MRC's own Good Research Practice (second edition, September 2005) is binding upon the PACE Trial Investigators and is unambiguous: on page 2 is to be found the following:

"The MRC expects ALL scientists, both clinical and non-clinical, funded by the Council (ie. MRC employees, visiting workers in MRC establishments, and recipients of MRC grants or training awards) to adopt the highest achievable standards in the conduct of their research. This means exhibiting impeccable scientific integrity and following the principles of good research practice".

The same MRC document states on page 3: "*Researchers must pay as much attention to perceived and potential conflicts of interest as to actual conflicts.* ***How one is perceived to act influences the attitudes and actions of others, and the credibility of scientific research overall****".*

The Research Governance Framework for Health and Social Care, Second Edition, 2005, warns at section 9.15 ("*Care and protection of research participants*") about: *"circumstances that might lead to conflicts of interest that may affect the independent judgement of the researcher(s)."*

The West Midlands MREC should (or ought to) have been concerned about dual or parallel relationships of the Investigators with the participants, for example if a researcher was currently also employed by the DWP (who are co-funders of the trial), or if participants have an insurance policy with an insurance company with which the researcher has a connection. **Such connections could have a significant influence on a participant's decision to join a research project, and therefore ought to have been declared**.

The Principal Investigators' "*circumstances that might lead to conflicts of interest"* include information about their association, consultation, hospitality and employment with insurance companies and the Department for Work and Pensions, every one of which might be considered to "*affect the independent judgement of the researcher(s)"*, yet initially the Investigators declared no financial or other conflicts of interest (see below).

Was the West Midlands MREC aware that the three Principal Investigators have substantial competing interests?

Fortunately for the PACE Trial Investigators, particularly for Professor Trudie Chalder, Professor Simon Wessely was a member of the Institute of Psychiatry/South London and Maudsley NHS Trust Working Party on Ethical Funding Sources which met on 20th July 2005 to review existing policy on acceptance of external research funding (Joint policy and guidance to research staff on the acceptance of external research funding, updated in March 2006), which provides guidance on the acceptance of funding from, for example, the DWP:

"The key principles identified by the Working Party were as follows:

"2.1 ***That research meeting only the highest scientific and ethical standards will be undertaken by staff and students of IoP and SLaM.***

"2.2 ***That…integrity of the conduct of the research and its results are not compromised.***

"2.5 That the nature of the research processes, ***including study design,*** *data analysis and publication of research findings* ***are transparent.***

"3.3 Questions to consider:

"What are the aims of the funding organisation? Are there any ethical issues that arise e.g. an association with…organisations that may have harmful consequences for health…?

"Is the nature of the funding organisation clear? Does there appear to be an attempt to conceal the aims…of the organisation?

"Is the funding organisation seeking to control the design and/or the data analysis? If they are, what are the risks to the integrity of the research?

"Does the funding organisation have a biased research agenda, for example, supporting projects leading to 'wanted' results?

"Is the decision-making process transparent? Is it clear who makes, and who may influence, funding decisions?".

How closely did Professor Chalder follow this guidance?

How "transparent" was the DWP decision-making process to fund the PACE Trial?

On 31st July 2007 the DWP was sent an email asking for information, including the following:

- a copy of the original proposal received by the DWP requesting funding for the PACE Trial
- documents that reviewed the request for funding of the PACE Trial
- documents explaining the DWP's reasons for agreeing to offer funding for the trial.

On 24th August 2007 the DWP replied by letter saying: "***The Department does not hold this information".***

On 1st October 2007 the DWP was asked to double check that it did not hold the requested information about its funding of the PACE Trial.

On 5th November 2007 the DWP replied by letter saying: ***"I am satisfied that this department does not hold the information that you request".***

Thus it can be said with certainty that the DWP has no record of the original application for funding of the PACE Trial; that the DWP has no record of how the application for funding of the PACE Trial was reviewed, and has no record of why it chose to fund the PACE Trial.

This is astonishing, given that the PACE Trial is the only clinical trial that the DWP has ever funded.

Clearly, therefore, the DWP seems to fail all the criteria from the "Joint policy and guidance to research staff on the acceptance of external research funding" set out above.

Could this lack of "transparency" concerning the funding -- using tax-payers' money -- by a Government body of an MRC clinical trial about which there is serious concern be in any way connected to the fact that the trial's Chief Investigator happens to be the DWP's lead advisor on the disorder in question?

There can be no doubt that there are substantial conflicts of interest on the part of numerous people involved with the PACE Trial, many of whom -- as noted above -- work for the medical and permanent health insurance industry and thus they cannot but have vested interests in pleasing their paymasters, whose aim on behalf of shareholders is thought by many not to pay out on a policy if they can possibly avoid doing so ("*UNUM stands to lose millions if we do not move quickly to address this increasing problem"*: UNUM's CFS Management Plan; Dr Carolyn Jackson, 4th April 1995). Examples of the failure of UNUMProvident to honour its obligations can be found in Appendix IV.

Prominent PACE Trial individuals who work for the insurance industry include Professors Peter White, Michael Sharpe, Simon Wessely and Trudie Chalder. Jessica Bavinton (a physiotherapist who used to work with Professor White and who co-authored the PACE Trial GET Manual with him) also does a lot of work for the same insurance companies. These facts are backed by written evidence.

This important issue of vested interests has been repeatedly raised in the House of Commons (for example in the 2006 Report of the Gibson Inquiry) and Members of the Scottish Parliament have written to Allied Dunbar about their concerns over Michael Sharpe's suitability to give an unbiased view when assessing people with ME/CFS; Sharpe has asked MSPs to withdraw their statements to Allied Dunbar about him.

With the support of Action for ME, funding of "rehabilitation" (ie. CBT/GET) in the NHS by commercial bodies, including PRISMA, began before 2002: "*One of the major patients charities (Action for ME) is aligning itself with a more evidence-based approach……Funding of rehabilitation by commercial bodies has begun in the UK (with organisations such as PRISMA) and is likely to continue"* (Functional Symptoms and Syndromes: Recent Developments. Michael Sharpe. In: Trends in Health and Disability. UNUMProvident 2002).

PRISMA is a multi-national healthcare company working with insurance companies; it arranges "rehabilitation" programmes (ie. GET) for those claiming on their insurance policies and it claims to be

especially concerned with long-term disability from the perspective of Government, service providers and insurance companies. **In the PRISMA company information, Simon Wessely is listed as a Corporate Officer; he is a member of the Supervisory Board, and in order of seniority, he is higher than the Board of Management.** Is it possible that Professor Wessely is recommending a management programme for "CFS/ME" patients which is known to be positively harmful for those with ME and which is provided by a company of whose Supervisory Board he is a member? However, on 28th July 2007 Simon Darnley , General Manager for Prisma Health (sdarnley@prismahealth.com) wrote to a correspondent: *"I would like to confirm that Professor Simon Wessely is not a corporate officer with the Prisma Health Group and in fact does not hold any position within the company at all. I am not sure where you heard this but it is not true"*.

The previous year, the same Simon Darnley from King's (who has responsibility for supervising the Prisma assessment and treatment programmes for all clients referred by insurance companies) gave Workshop 9 at the British Association for Behavioural and Cognitive Psychotherapies Congress in Warwick, in which he said: "*There is increasing focus on Return to Work with the success of programmes such as…the privately funded Prisma Programme. Increasing numbers of CBT therapists are involved through these programmes in helping people back to work…..**However, with clients who are not currently working, clinical progress may be limited because therapists have insufficient influence on the non-clinical maintaining factors (e.g. financial and employment issues)**….**We will explore the therapeutic implications of working within a politically generated environment, asking 'What happens when you mix politics with therapy',* **(and)** ***'How ethical is it to use motivational techniques when the result is cessation of benefit?' "*** (http://www.babcpconference.com/archive/conference_archive/warwick2006_2.htm#W9). This should be borne in mind when reading the section below on "Data-gathering for non-clinical purposes". It remains to be clarified why the DWP decided to provide funding for the PACE Trial and how it justifies the expense to the tax payer and, indeed, what the Department expects in return for such an investment of public money.

At the Trial Steering Committee meeting on 22nd April 2004, all members present were asked to declare any conflict of interest. **No financial conflicts of interest were declared and it was agreed that no-one present had any other substantial or material conflict relevant to their work on the PACE Trial. Amongst those present were Professors Peter White, Michael Sharpe and Trudie Chalder.**

On 18th June 2004, Professor Peter White wrote to members of the PACE Trial Steering Committee asking them to declare any conflicts of interest -- particularly of a financial nature -- regarding the PACE Trial, with the written promise that such information *"will be kept securely"*.

On 22nd July 2004, Professor Mansel Aylward, who it will be recalled was then Chief Medical Adviser to the Department for Work and Pensions and a member of the PACE Trial Steering Committee, replied saying: "*It seems I had overlooked responding to your letter of 18 June. I apologise and am remedying that here. I thus write to confirm that I have no conflicts of interest, particularly in respect of any of a Financial* (sic) *nature regarding the PACE trial"*. Such a statement seems misleading, because Aylward had by then been appointed to the Chair in Psychosocial and Disability Research at the University of Cardiff that is funded by the insurance company UNUMProvident and by 1st July 2004 it was public knowledge that he was to head the UNUMProvident Centre for Psychosocial and Disability Research and that he was to take up this post when he left the DWP. Aylward could not have been unaware that UNUMProvident was already financing his next employment, and that UNUMProvident has one of the worst track records for denying claims made by people unable to work because of ME/CFS.

Aylward's job at Cardiff appears to be centred around ensuring people with "CFS/ME" are removed from disability payment and are returned to work *"with or without symptoms"* according to UNUM's "Chronic Fatigue Syndrome Management Plan" referred to above, which clearly states: *"Diagnosis: Neurosis with a new banner"; "Attending physicians (must) work with UNUM rehabilitation services in an effort to return the patient/claimant back to maximum functionality with or without symptoms".*

Professor Aylward seems to have an unfortunate track record in relation to accuracy – see Appendix V.

There is another curious aspect concerning conflicts of interest of the PACE Trial Investigators. The Minutes of the Joint meeting of the Trial Steering Committee and the Data Monitoring and Ethics Committee held on 27th September 2004 record that Professor White confirmed that letters had been received from all TSC members confirming that no-one had any conflicts of interest.

This is a serious issue, because there is written evidence that Professors Peter White, Michael Sharpe and Trudie Chalder may have been less transparent than was required of them.

Notably, the same people (Professors White, Sharpe and Chalder) were involved with the production of the NHS Plus Guideline on returning people with "CFS/ME" to employment (Occupational Aspects of the Management of Chronic Fatigue Syndrome: a National Guideline; October 2006), where they also declared no conflict of interests.

On 20th November 2008 the Department of Health confirmed (in writing) in relation to the NHS Plus Guideline about Professors White, Sharpe and Chalder: "*I can confirm that the guideline contributors gave written confirmation that they had no conflicts of interest".*

Since it was believed that Professors White, Sharpe and Chalder all did have obvious and serious conflicts of interest and since any such conflicts had been denied by them, representations were made questioning why their known conflicts of interest had been denied.

Following these representations, on 23rd December 2008 a remarkable revelation was made – in writing – by Dr Ira Madan, Director of Clinical Standards, NHS Plus (who, with Wessely and Chalder, is based at King's College):

"*The Department of Health have asked me to investigate your concern that one of the guideline development group members, Professor Trudie Chalder, and the two external assessors, Professor Michael Sharpe and Professor Peter White, had conflicts of interest whilst involved in the production of the guideline.* ***I can confirm that I was aware of the potential for competing interests that you have stated. The roles that Professor White, Professor Sharpe and Professor Chalder have undertaken for the agencies and companies that you stipulate*** **(i.e. the DWP and the medical and permanent health insurance industry)** ***were in the public domain prior to the publication of the NHS Plus guideline.*** *I am content, as the Director of that guideline, these potential competing interests did not in any way influence the synthesis of the evidence or the guideline recommendations".*

There is thus written confirmatory evidence from Dr Ira Madan that Professors White, Sharpe and Chalder all <u>did</u> have what she referred to as "*competing interests*", but that she was "*content*" about the situation.

However, the MRC PACE Trial Minutes twice record that these same people had declared <u>no</u> conflicts of interest (recorded first in the Minutes dated 22nd April 2004 and again in the Minutes dated 27th September 2004).

Thus there is written evidence -- from Dr Madan at the Department of Health -- illustrating how the normal rules of independent peer review and conflicts of interest seems to be suspended when it comes to the "evidence-base" for CBT/GET in people with ME/CFS because in relation to the NHSPlus Guidelines, two researchers were allowed to sit in judgment on their own publications, with the prior knowledge and permission of Dr Ira Madan.

Furthermore, they were not required to make conflict-of-interest declarations, even though their conflicts were known about by Dr Madan. This is not peer-review as the rest of the scientific world understands it.

However, Professors White, Sharpe and Chalder seem to have had a change of mind and they then did declare and list serious conflicts of interest in relation to exactly the same material issues in the MRC PACE Protocol:

"PDW has done voluntary and paid consultancy work for the Departments of Health and Work and Pensions and legal companies and a re-insurance company. MCS has done voluntary and paid consultancy work for government and for legal and insurance companies. TC has done consultancy work for insurance companies, is the author of Coping with Chronic Fatigue published by Sheldon Press and co-authors Overcoming Chronic Fatigue with Mary Burgess published by Constable and Robinson." (http://www.biomedcentral.com/1471-2377/7/6).

Thus there is conflicting information provided by the Principal Investigators; is this the high standard of integrity required in an MRC clinical trial?

A search of PubMed for Professor White's own declarations of interest just for the years 2004 to 2009 reveals that in many of the papers, he did not declare any competing interests at all, despite clear warnings from the journals that *"Authors are responsible for recognising and disclosing financial and other conflicts of interest that might bias their work…**authors must disclose any commercial associations that might impose a conflict of interest in connection with the study**"* (Journal of Rehabilitation Medicine, in which Peter White published an article on Chronic Fatigue Syndrome in 2008:40(10):882-885).

Given the long-time involvement of so many people involved in the PACE Trial (especially the Principal Investigators and Professor Wessely) with the medical and permanent health insurance industry and with Government agencies whose intention is understood to be to target people with ME/CFS in order to remove them from benefits, there is legitimate concern that such conflicts of interest will direct the outcome of the trial.

The Gibson Report of 2006 expressed concern about these competing financial interests at page 31, section 6.3:

"***At present, ME/CFS is defined as a psychosocial illness by the medical insurance companies. We recognise that if ME/CFS remains defined as psychosocial then it would be in the financial interests of the medical insurance companies.***

"***There have been numerous cases where advisors to the DWP have also had consultancy roles in medical insurance companies, particularly the company UNUMProvident.***

"Given the vested interest private medical insurance companies have in ensuring CFS/ME remains classified as psychosocial illness, there is blatant conflict of interest here.

"This Group finds this to be an area for serious concern and recommends a full investigation by the appropriate standard body" (http://erythos.com/gibsonenquiry/Docs/ME_Inquiry_Report.pdf).

Those parliamentarians who expressed this concern included the former Chairman of a House of Commons Science and Technology Select Committee and former Dean of Biology; a member of the Home Affairs Select Committee; a Minister of State for the Environment; a former President of the Royal College of Physicians; the Deputy Speaker of the House of Lords, and a former Health Minister and Honorary Fellow of the Royal College of Physicians.

To date, nothing whatever has been instituted to remedy this unacceptable situation.

Fraudulent research (Cargo cult science)?

Cargo cult science is a term used to describe work that has the semblance of being scientific, but whilst such studies follow all the apparent precepts of scientific investigation, they are missing something essential: they lack scientific integrity. Cargo cult scientists conduct flawed research that fails to produce useful results.

Physicist and Nobel Laureate Richard Feynman summarised it thus: "*We really ought to look into theories that don't work, and science that isn't science. It's a matter of scientific integrity…..although you may gain some temporary fame and excitement, you will not gain a good reputation as a scientist if you haven't tried to be very careful in this kind of work. And it's this type of integrity, this care not to fool yourself, that is missing to a large extent in much of the research in Cargo Cult Science….the idea is to try to give all of the information to help others to judge the value of your contribution; not just the information that leads to judgment in one particular direction"* (Engineering and Science: June 1974:10-13).

The Times Online reports disconcerting findings about scientific studies: "*Faking scientific data and failing to report commercial conflicts of interest are far more common than previously thought, a study suggests".* Dr Daniele Fanelli of the University of Edinburgh, who carried out the investigation, says: "*Increasing evidence suggests that known frauds are just the tip of the iceberg"*. The article reports: "*The results paint a picture of a profession in which dishonesty and misrepresentation are widespread".* It concludes: "*Misconduct was far more frequently admitted by medical or pharmaceutical researchers than others, supporting fears that the field of medical research is being biased by commercial interests"* (One in seven scientists say colleagues fake data. Times Online. Hannah Devlin, June 4th 2009). The article may come as no surprise to the ME/CFS community.

Is the PACE Trial "Cargo Cult Science"? Time will tell, but it seems that the PACE Trial may not be being carried out within the normal confines of scientific exactitude.

Conflicting information

Conflicting information permeates the PACE Trial Manuals and this is evident in the quotations in Section 4 below, so just a few illustrations are given here. The researchers' inconsistencies are notable.

The NICE Guideline on "CFS/ME" states: "***The GDG did not regard CBT or other behavioural therapies as curative*** *or directed at the underlying disease process"* (Full Guideline, page 252). Physiotherapist Jessica Bavinton (who used to work with Peter White) was a member of the NICE Guideline Development Group and as such, she agreed with -- and signed up to -- that statement, but she also wrote the PACE Trial Manuals on GET and contributed to the Manuals on CBT, which contradict the NICE Guideline.

Peter White claims that *"a full recovery is possible"* (Psychother Psychosom 2007:76(3):171-176); **the participants' CBT Manual informs people that the PACE Trial therapies are curative** and that "*many people have successfully overcome their CFS/ME"* with such behavioural interventions ("Information for relatives, partners and friends", page 123). This appears to be untrue for people with ME/CFS and it is unethical for the content of the Manuals to mislead participants. **Moreover, Simon Wessely himself claims that neither CBT nor GET is remotely curative and that many patients do not benefit from them.**

That many patients with ME/CFS do not in fact benefit from these interventions is already a matter of record, being the published views of the keenest CBT proponents themselves:

- CBT and GET are only *"modestly effective". "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)

- *"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"* (http://www.drlapp.net/news.htm).

The PACE Trial Manuals, however, make it clear that there is no underlying disease process and that the perceived disease is reversible by the behavioural therapy used in the PACE Trial.

The PACE Trial message is that exercise **prevents** various diseases, not just "CFS/ME": the GET Manual for therapists states on page 24*: "As well as direct impact upon CFS/ME, exercise has also been shown to have a strong role in the* ***prevention*** *of various diseases such as coronary heart disease, stroke, cancer, and type II diabetes, as well as reducing the risk of premature death by 20-30%".*

So in one section, the authors of the PACE Trial Manuals state that GET is "*preventative"* for "CFS/ME", but then the Manuals warn therapists that they may be treating sportspeople who are used to exercising, and that these people may be problematic to deal with in that they may wish to over-exercise. If exercise (and especially GET as claimed) is "preventative", why have people who have exercised succumbed to the disorder? Such illogical statements pervade the Manuals.

The Trial Manuals are replete with other internal inconsistencies and contradictions.

For example, one of the arms of the Trial (pacing) is believed to be anathema to the Chief Investigator, Professor Peter White. This may be because the need for pacing implies an underlying pathological process, a concept that militates against his belief that ME/CFS is a behavioural disorder.

In 2002, the same year that he applied for funding for the PACE Trial, Professor White explained why he and some of his like-minded colleagues resigned from the Chief Medical Officer's Working Group that reported on "CFS/ME" in 2002: "*some clinicians could not agree to recommend 'pacing' on the basis of patient group experience alone…..some clinicians believed that the report over-emphasised the severity and chronicity of CFS to the extent of suggesting that recovery was unlikely, when the evidence shows that not to be true. The report's recommendation omitted any suggestion that cognitive behaviour therapy and graded exercise therapy should be more readily available. These recommendations were obfuscated by equally promoting 'pacing'.* ***The theoretical risk of pacing is that the patient remains trapped by their symptoms in the envelope of ill-health"*** (Postgraduate Medical Journal 2002:78:445-446).

However, in his PACE Trial Protocol (2006 version), Professor White states: "*All the participating clinicians regard all the four treatments* (including pacing) *as potentially effective"*, which contradicts his published views.

In relation to APT, the PACE Trial literature informs participants that Adaptive Pacing Therapy (APT) is *"strongly"* recommended by the patients' charities, but on searching the Action for ME website for either "adaptive pacing therapy" or "APT", neither term comes up.

To misinform participants in such a manner is surely unacceptable, but misleading material occurs throughout the PACE Trial literature.

Notably, whilst therapists are trained to "psych-up" patients on the CBT and GET arms of the Trial for their triumphant return to work, patients on the APT arm of the Trial are <u>not</u> to be "psyched-up" to return to work.

It seems that, in comparison with CBT and GET, the Trial Investigators do not mind if APT fails in getting participants back to work (which might more readily occur if there is no up-beat enthusiasm conveyed to participants in the APT arm of the PACE Trial).

If CBT and GET do succeed in returning patients on the PACE Trial to employment, the question remains as to whether or not the "recovered" patients ever suffered from ME/CFS in the first place, because there is no credible evidence that people with ME/CFS do recover.

The PACE Trial Identifier states at Section 2.3:

"Because CBT and GET are based on graded exposure to activity or exercise, they may preferentially improve disability, whilst APT, being based on the theory of staying within the limits of a finite amount of "energy", may improve symptoms, but at the expense of disability" (emphasis added).

Thus there is clear antipathy shown by the Trial Investigators towards APT, **yet while the PACE Trial Protocol states that pacing has no scientific basis, the therapists' Manuals (though not the participants' Manuals) state that SSMC, CBT and GET may nevertheless all be considered to be forms of pacing.**

This is an extraordinary notion. Pacing is common sense and it does not involve planned exercise.

Common sense cannot be turned into a "therapy".

APT, however, seems not to be "pacing", since it seems to involve achieving and sustaining "targets"; it seems that the Trial Investigators were seeking to placate participants by referring to APT as "pacing" (which participants know to be helpful) when in reality APT is a vehicle for incremental aerobic (or, according to the Investigators, "paced") exercise.

There was obvious concern about APT expressed at the Joint meeting of the Trial Steering Committee and the Data Monitoring and Ethics Committee held on 27th September 2004 with members showing doubt about how APT should be defined and how it could be assessed in a trial:

"*As this is a therapy being designed specifically for PACE that has never been previously tested in a randomised trial for patients with CFS/ME, this manual requires slightly more thorough piloting than the more established therapies. As a consequence, the manual might be altered even after the MREC submission has been made"* (Minutes, section 9).

Commenting in ME Essentials on the ME Association's Big Survey of management interventions, Professor Christine Dancey from the Chronic Illness Research Team, School of Psychology, University of East London, points out about pacing:

"*1522 people had tried pacing as a technique… when we look at the numbers, we find far more people improved than expected by chance. This is not just an effect of random variation in symptoms.* ***So, with pacing, the likelihood is that it will help them, and is unlikely to harm them".***

This may be yet more evidence that may not concur with the PACE Trial results.

Data-gathering for non-clinical purposes

Throughout the therapists' Manuals there are numerous references to Job Centres and about returning participants to work. Coercing physically sick people back to work by purveying misinformation about their illness is held by many people to be unacceptable.

Should it be the purpose of a clinical trial to be so focused on Job Centres and to aim to get participants off State benefits? Clinical trials are supposed to be directed towards improving a patient's health and quality of life, not gambling with them to achieve financial benefits for the State or for the insurance industry.

An article in 2002 by Peter Pallot on health insurance gives examples of the risks of chronic illnesses such as ME/CFS for medical insurance companies: referring to the CMO's recognition of ME/CFS as a genuine disorder, Pallot said:

"Official recognition has not brought clarity for insurers. Take for instance a 30 year old who succumbed aged 30 when earning £75,000 a year. The policyholder might be in line to get two-thirds salary -- £50,000. Over 35 years, if the condition never resolved, the insurer would be paying out £1.75 million. ***Re-naming the condition CFS and discarding earlier labels including ME was helpful. 'Syndrome' implies a range of causes and symptoms****. The company's exposure to chronic fatigue claims has pushed it into a very proactive approach. We get Prisma to talk to the individual and also to the partner; Prisma will work out a programme. Until recently, the role of IP (income protection) providers stopped at paying claims. Now they are initiating intervention"*
(http://www.hi-mag.com/healthinsurance/article.do?articleid=20000081634).

Could there be a more clearly expressed reason for the determination of Wessely School members who do so much work for the medical insurance industry to deny that ME/CFS exists and to oppose the evidence that it is a serious, multisystem organic disease from which full recovery is unlikely? If objective evidence of pathology were to be acknowledged, that would remove the insurers' assertion that "CFS/ME" is a psychosocial disorder.

The PACE Trial literature contains numerous references to what seems to be simply data-gathering for non-clinical purposes (as opposed to supporting patients in dealing with a devastating disorder). For example, the Trial Identifier states at section 3.9: "*The Client Service Report Inventory (CSRI), adapted for use in CFS, will measure hours of employment/study, wages and benefits received, allowing another more objective measure of function (and) the CSRI will measure disability benefits received, shown to predict poor outcome with CBT"* (the CSRI is a method of costing mental health interventions and is to be found in "Measuring Mental Health Needs"; ed: Thornicroft G; London, Gaskell, 2001).

Is importing non-clinical and non-scientific values into a clinical trial be ethical, especially when there is no guarantee that the Principal Investigators will not use the information gained for purposes other than clinical? For example, participants are asked if they are in receipt of benefits, but what has a participant's financial status to do with a clinical trial? Also, participants are asked about their "coping strategies". At first glance, this may seem to be patient -orientated and thus commendable, but then participants are asked if their coping strategies include being a member of an ME self-help group such as the ME Association (the Wessely School believe -- on no credible evidence – that, along with being in receipt of State benefits, membership of a self-help group is a "*perpetuating factor*" that militates against recovery).

Seeking such non-clinical information which is known to be a particular facet of the Investigators' personal beliefs about people with ME/CFS invites the possibility that such information will be used to perpetuate the Investigators' personal beliefs.

Insufficient testing of participants' physical ability

The PACE Trial participants' physical ability was to be assessed by requiring them to walk on level ground for six minutes. "*A six minute walking test will tell us how physically able you are"* (Participation Information Sheet for PACE Trial, SSMC Manual, page 27; the six minute baseline assessment on a level surface is also mentioned in the PACE Trial Protocol, Final Version 5, page 201). For patients with ME/CFS, this is inappropriate (see Section 2 above).

Initially, the Trial Investigators planned to use objective measures of physical ability at the conclusion of the Trial (the cost of the Actiwatch sensors was included in the funding application), but Peter White decided that any actigraphy measurements should not be taken at the end of the Trial. As Tom Kindlon from Ireland points out, this is notable, since Professor White is aware that self-reported (ie. subjective) improvements may not match real (ie. objective) improvements and equally that there are discrepancies between subjective and objective measures of activity (http://www.biomedcentral.com/1471-2377/7/6/comments#333618).

Not to use objective measures of improvement (such as actigraphy; physiological measurements; return to employment) is deemed by many to be scientifically inexcusable in an MRC trial that specifically sets out to assess the efficacy of the interventions employed in the trial.

It was conclusively demonstrated in 1999 that patients with ME/CFS reach exhaustion more rapidly than normal subjects, that they fail to recover properly from fatiguing exercise and that this failure is more pronounced 24 hours after exercise (L. Paul et al. European Journal of Neurology 1999:6:63-69).

Therefore, a single test is unlikely to reveal any abnormality and **serial testing is essential because it is the second test that provides objective evidence of abnormality in ME/CFS patients and of their inability to work.**

This is clear from the literature, and was unambiguously demonstrated at the 8th International Association of Chronic Fatigue Syndrome (IACFS) Conference held at Fort Lauderdale, Florida, from 10th-14th January 2007. Margaret Ciccolella and Professor Christopher Snell et al from Stockton, CA, demonstrated that patients show extreme abnormalities in a next-day / second session of exercise. They do not recover in 24 hours. In one study, only one patient had recovered to baseline within 48 hours. These changes in serial testing point to a significant and confirmable physical abnormality, verifying the cardinal symptom of post-exertional malaise. This test / retest exercise test is 100% objective and can prove to the insurance companies and agencies of the State that ME/CFS is neither malingering nor faking. In ME/CFS patients, the measurements declined by about 25%, far more than in other significant diseases such as COPD (chronic obstructive pulmonary disease) and even heart failure.

Given that Peter White has published a paper showing that TNFα remains elevated three days after exercise in "CFS/ME" patients (JCFS 2004:12 (2):51-66)**, it is indisputable that he knows that any outcome measures need to include serial testing of physical capacity, and should also include post-exercise immunological testing, yet no such testing was scheduled in the PACE Trial.**

Post-exertional malaise following exercise challenge in ME/CFS patients results in fatigue, light-headedness, vertigo, joint pain, muscle pain, cognitive dysfunction, headache, nausea, trembling, instability, and sore glands, therefore 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.

Professor Mark VanNess from the University of the Pacific demonstrated that maximum aerobic capacity (VO_2 peak) is reduced in ME/CFS compared with sedentary controls.

Also presented at the same conference was the work of Dr Vance Spence (University of Dundee) on inflammation and arterial stiffness in patients with ME/CFS. This work looked at inflammatory factors (free radical by-products and C-reactive protein, an inflammatory marker) and found abnormally high levels of free radical by-products and C-reactive protein in patients but not in controls. C-reactive protein levels were significantly correlated with increased arterial stiffness. The logical consequences of increased arterial stiffness are exercise intolerance and diastolic (cardiac) dysfunction.

According to Dr Tae Park from South Korea, the bright spots on MRI scans of some ME/CFS patients are evidence of an "*arteriolar vasculopathy*" or a blood vessel disease. He believes ME/CFS is a "*systemic micro-*

vascular inflammatory process" – a process that would affect not only the brain or the heart or the muscles, but potentially every organ and system in the body.

Dr Park found not only capillary inflammation and perivascular cuffing (the accumulation of immune cells that surround injured blood vessels), but that all the ME/CFS patients in his study demonstrated remarkably reduced renal blood flow. He pointed out that diabetics with renal vascular disease also complain of profound fatigue.

The remarkable similarity in the brain images of patients with ME/CFS and multiple sclerosis was also noted.

Studies by Professor Kenny De Meirleir et al (Belgium) found that the majority of ME/CFS patients had increased rates of RNase-L activity (83%), RNase-L fragmentation (88%) and a massive 95% had increased elastase levels. These abnormalities could contribute to the muscle symptoms seen in ME/CFS.

Dr James Baraniuk from Georgetown University, Washington DC described the (quote) *"unbelievable*" finding of unique markers in the cerebrospinal fluid of ME/CFS patients that are completely absent from the control group. The proteomic biosignature of ME/CFS in the cerebrospinal fluid shows:

1. a protease / antiprotease imbalance is present: alpha 2 macroglobulin (anti-protease) and orosomucoid 2 (anti-protease); this implicates increased elastase production

2. several proteins suggest that amyloid deposition in the blood vessels of the brain is causing micro-haemorrhaging (amyloidosis is the deposition in the tissues of a starchy, waxy protein substance; the organs most affected are the liver, kidneys, spleen and heart; it occurs in conditions of chronic inflammation)

3. one protein present suggests altered (increased) rates of apoptosis (ie. programmed cell death, a well-documented finding in ME/CFS)

4. another protein present suggests free radical production is occurring

5. another protein suggests problems with vasoconstriction and endothelial damage (pigment epithelial derived factor and endothelial proliferation associated with vascular dysregulation)

6. another protein is associated with inflammation.

One protein that was found – keratin – is of particular interest: it is associated with inflammation of the leptomeningeal cells in the membranes covering the brain and spinal cord. **This proteome is not found in healthy controls.**

Dr Jonathan Kerr from London stated that his gene expression studies are finding three main abnormalities in ME/CFS patients: these involve the immune system, mitochondrial function and G-protein signalling.

As noted in Section 2 above, various genes are upregulated in ME/CFS – those associated with apoptosis, pesticides, mitochondrial function, **demyelination** and viral binding sites. Kerr mentioned three genes in particular: gelsolin, which is involved in apoptosis and amyloidosis; one that is upregulated by organophosphates, and **a mitochondrial gene involved in the demyelination of nerves.**

The importance of sub-typing "CFS" was recognised and emphasised.

Information on other abnormalities that have been demonstrated in ME/CFS patients, including abnormal brain perfusion, more evidence of inflammation, mitochondrial dysfunction, immune system disruption, and vascular problems that was presented at the Florida research conference can be found at http://www.meactionuk.org.uk/Facts_from_Florida.htm.

Using neuroimaging techniques, several groups have identified neuro-anatomical abnormalities in ME/CFS patients. These include reduced regional blood flow, anatomical abnormalities in cortical and sub-cortical regions and reduced glucose metabolism (Marie Thomas and Andrew Smith. The Open Neurology Journal 2009:3:13-23).

It is impossible to summarise over 5,000 papers in one document, but the evidence of organic pathology in ME/CFS is extensive. For example, the wealth of scientific biomarkers that distinguish ME/CFS from "chronic fatigue" (a term used interchangeably with "CFS/ME" by the Wessely School) include the following:

- abnormal brain scans (SPECT & PET scans) and MRI scans that are consistent with organic brain syndrome, showing focal demyelination and/or oedema in the sub-cortical area
- a dysregulated HPA axis
- a dysregulated antiviral pathway (RNase-L)
- cardiac abnormalities
- abnormal capillary flow
- low circulating blood volume
- abnormal ergometry test (indicating immediate anaerobic threshold)
- haemodynamic instability
- abnormal immune profile
- gene profiling – there are more abnormal genes in ME/CFS than there are in cancer. In the US, Sorensen et al demonstrated that expression of several complement genes remains at a higher level in ME/CFS subjects before and post-exercise, which may lead to uncontrollable inflammation-mediated tissue damage. In the UK, Kerr demonstrated differential expression in 88 genes [85 up-regulated and 3 down-regulated] indicating haematological disease and function, immunological disease and function, cancer, cell death, and infection [J Infect Dis 2008:197(8):1171-1184], all of which are seen in ME/CFS but not in states of psychiatric fatigue, ie. "CFS/ME".

Possible biomarkers discussed at the Reno conference mentioned above include the following:

- ATP profiling of ion channel receptors
- Mitochondrial Energy Score
- Cytokine and chemokine analysis
- Near infrared
- EEG profiles
- Low molecular weight RNaseL
- HLA haplotype 4-3-53, VIP, C4a
- Antigliadin and anticardiolipin antibodies.

Professor Lapp's Reno summary (http://www.drlapp.net/news.htm) records that:

- the sympathetic nervous system is more active than the parasympathetic system in ME/CFS

- the metabolic, adrenergic and immune ion channel receptors were up-regulated for days after exercise in people with ME/CFS, with virtually no up-regulation in healthy controls -- metabolic, adrenergic and immune ion channel receptor mRNA markedly increases in people with ME/CFS or FM but not in healthy controls

- neuropeptide Y (NPY), a neurotransmitter that is concentrated in sympathetic nerve endings is elevated in people with ME/CFS in relation to stress much more than in normal controls

- numerous cytokines were significantly different in subject and controls

- IL8 and IL15 were decreased in patients with ME/CFS, while the pro-inflammatory cytokines (TNFβ, IL1α, IL1β and IL6) and Type 2 cytokines (IL4, IL5) were increased in ME/CFS, and the anti-inflammatory cytokine IL13 was reduced: this is consistent with the Th2 or up-regulated immune pattern usually seen in ME/CFS

- bowel dysfunction (dysbiosis, leaky gut, viral infections of the gastric mucosa) is frequently seen in ME/CFS and there is also a Th1/Th2 immune imbalance. Th1 (normal immunity) is antagonistic to the Th17 immune axis. Th17 cells are crucial regulators of inflammation and autoimmunity, and alterations of the Th17 pathway are frequently associated with intestinal disorders such as **irritable bowel syndrome**. Th17 cells produce IL17F protein and a variant known as His161Arg, which confers protection against inflammation**. His161Arg was found in only 6% of people with ME/CFS.** This suggests that the Th17 axis and intestinal dysfunction are involved in causing inflammation and possibly in the pathogenesis of ME/CFS

- ATP is markedly reduced in ME/CFS, which can explain many of the symptoms seen in the disorder – in fact, the severity of illness is directly related to the level of intracellular ATP

- changes on the brain MRI correlated with symptoms – using regression analysis, significant correlations could be made between MRI changes and illness severity: cerebellar changes correlated with coordination and motor function; frontal changes correlated with fatigue and impaired motor function, and this study correlates known ME/CFS symptoms with specific areas of the brain, affording further validity to the disorder

- 61% of cases seen in one study had an elevated antigliadin antibody (wheat intolerance) and anticardiolipid antibody, MMP9, and TGFβ-1 were also abnormal in many cases

- a greater proportion of female patients with ME/CFS had chronic pelvic pain.

The conference confirmed that multiple bodily systems are involved in ME/CFS.

There is also published evidence that recovery rates for oxygen saturation are 60% lower than those in normal controls; evidence that the average oxygen uptake is only 15.2 ml/kg/min, whilst for controls it is 66.6 ml/kg/min; evidence of reduced lung function in all parameters tested, and conclusive evidence of delayed recovery of muscles after exercise.

In light of the above, for the PACE Trial Investigators to assess a participant's physical capability (and thus their alleged ability to work) on a six minute walking test would seem to be highly questionable.

However, in his letter in response to an article that was critical of the use of exercise in ME/CFS that resulted in exacerbations (J Rehabil Med 2008:40:241-247), Peter White wrote: "*A central concept of GET is that patients maintain their level of exercise as much as possible even after a CFS/ME setback. This is to reduce the many negative consequences of rest and allow the body to habituate to the increased in activity"* (J Rehabil Med 2008:doi:10.2340/16501977-0261).

This goes beyond even what he said in the GET Manual for therapists, namely: "*A central concept of GET is to maintain exercise as much as possible during a CFS/ME setback".*

It is notable that advising exercise during a relapse is contrary to what Peter White said in his presentation on 15th April 1992 at the Pfizer/Invicta symposium held at Belfast Castle (Eradicating "Myalgic Encephalomyelitis), where in his guidelines for a gradual exercise programme he said: ***"Do not exercise if clinically active infection is present"***.

(He also said at that same meeting, however, that (i) *"there has never been any evidence that the condition is associated with inflammation of the central nervous system"* (ii) *"the only findings of note have been that fatigue is associated with…an exaggerated perception by patients of the effort they are exerting"*; that a graded exercise and activity programme *"might meet with some resistance in view of the widely believed myth that avoidance of exertion is vital"* and that *"exercise should be aerobic"*).

The PACE Trial has no serial checks on the participants' immune parameters even though, as mentioned, Professor White has published a paper on this aspect (ie: Immunological changes after both exercise and activity in chronic fatigue syndrome: a pilot study. White PD, KE Nye, AJ Pinching et al. JCFS 2004:12 (2):51-66). In that article, White et al stated:

"We designed this pilot study to explore whether the illness was associated with alterations in immunological markers following exercise. 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-β1 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.*

"These data replicate three out of four previous studies finding elevated TGF-β in subjects with CFS.

"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 preliminary data suggest that 'ordinary' activity (ie. that involved in getting up and travelling some distance) may induce anti-inflammatory cytokine release (TGFβ), whereas more intense exercise may induce pro-inflammatory cytokine release (TNF-α) in patients with CFS".

This important information seems to have been withheld from participants and therapists alike (the Therapists' Manual on GET is dismissive of studies showing immune dysfunction in ME/CFS).

In the light of this knowledge, it is notable that there seems to be a disregard of safety for GET participants, even though the Chief Investigator (Peter White) is aware that <u>three days after exercise</u>, TNFα remains elevated and that this probably accounts for the "*sickness behaviour*" and "*weakness, malaise, listlessness and inability to concentrate*".

Known biases in Random Controlled Trials may not have been avoided in the PACE Trial

The PACE Trial Identifier claims at section 1.1 that the trial is a random controlled trial (RCT).

The RCT is the recognised way of reducing bias, but Jadad and Enkin's classic treatise on the known biases that may occur even in an RCT is essential reading for anyone considering the PACE Trial (Randomized Controlled Trials. Alejandro Jadad and Murray Enkin. Oxford: Blackwell Publishing, 2007; 1st published in 1998). Jadad currently advises the WHO as a member of its Strategic Advisory Group of Experts and Enkin is Professor Emeritus, Clinical Epidemiology and Biostatistics, McMaster University, Toronto.

The second edition challenges over-reliance on the RCT and includes a chapter on the ethics of RCTs.

The following quotations from the second edition may be relevant when considering the PACE Trial:

"Randomization, if done properly, can keep study groups as similar as possible….Random allocation does not, however, protect RCTs against other types of bias (and) important research studies…have confirmed that RCTs are vulnerable to many types of bias throughout their entire life span.

"Biases in clinical trials most often lead to an exaggeration in the magnitude or importance of the effects of the new interventions.

"Selection bias can occur if some potentially eligible individuals are selectively excluded from the study.

"There are many ways in which randomisation can be subverted by investigators.

"Perhaps one of the least recognised forms of bias in an RCT is hidden in the choice of the question that the trial intends to answer (which) may have profound effects on its external validity, or generalisability. This bias can take many forms.

"Hidden agenda bias occurs when a trial is mounted, not to answer a question, but in order to demonstrate a pre-required answer….Closely related to this is the self-fulfilling prophecy bias, in which the very carrying out of the trial ensures the desired result.

"Closely related to this is the funding availability bias where studies tend to concentrate on questions that are more readily fundable, often for a vested or commercial interest.

"Regulation bias: This is sometimes referred to as the Bureaucracy bias. It occurs when (institutional review boards) allow or even encourage studies that may not be scientifically or socially valid…..Complicated 'informed consent' regulations may block the participation of many otherwise eligible subjects and hence bias the results.

"The wrong research design can produce misleading answers.

"Population choice bias: ***"The sample population studied can have a major effect on the generalisability of an RCT. If the sample is overly restrictive (gender bias; age bias; special circumstances bias; recruitment bias), the results may not be generalisable to people who do not belong to the groups****.*

"Severity of illness bias is an important subgroup of the sample choice bias. Patients with a mild form of an illness may not respond in the same way as those with a more severe form.

"Comparison choice (or control group) bias: If an intervention is compared to a poorly chosen control group, it can erroneously appear to be more effective than it really is. *An obvious way to make an intervention appear to be more effective than it really is would be to choose an ineffective comparison group.*

"Outcome choice bias: Sometimes RCTs evaluate outcomes that are easy to measure, rather than the outcomes that are relevant (measurement bias).

"One variant of this is the time term bias in which short-term outcomes are measured rather than the important long-term outcomes".

Other biases listed include withdrawal bias; bias introduced by inappropriate handling of withdrawals, drop-outs and protocol violations; missing data bias; publication bias; moral bias; values bias; printed word bias (when a study is overrated because of undue confidence); **prominent author bias (when the results of studies published by prominent authors are overrated, including esteemed author bias and esteemed professor bias)**; multicentre collaborative trials (when the results are overrated); vested interest bias; cherished belief bias and empiricism bias ('I am an epidemiologist' bias).

The authors conclude: "***RCTs can never be completely objective. They should be carried out with humility; the investigator should be up-front, explicit and transparent as possible about his or her motivations for choosing to carry out the trial".***

Where is the evidence of this in the PACE Trial?

According to Ioannidis (PLoS Medicine 2005:2:8:e124), *"a research finding is less likely to be true when…there is greater flexibility in …definitions (and) when there is greater financial and other interest and prejudice".*

Ioannidis defined bias as *"the combination of various design, data, analysis and presentation of factors that tend to produce research findings when they should not be produced".*

He said: "*Conflicts of interest and prejudice may increase bias…**Scientists in a given field may be prejudiced purely because of their belief in a… theory or commitment to their own findings**…Such conflicts may lead to distorted reported results and interpretations. **Prestigious investigators may suppress via the peer review process the appearance and dissemination of findings that refute their own findings, thus condemning their field to perpetuate false dogma….Prejudice may prevail in a hot scientific field, further undermining the predictive value of its research findings. Highly prejudiced stakeholders may even create a barrier that aborts efforts at obtaining and disseminating opposing results**".*

Ioannidis continued: *"Let us suppose that in a research field there are no true findings at all to be discovered. **History of science teaches us that scientific endeavour has often in the past wasted effort in fields with absolutely no yield of true scientific information…Of course, investigators working in any field are likely to resist accepting that the whole field in which they have spent their careers is a 'null field'. However, …advances in technology and experimentation may lead eventually to the dismantling of a scientific field"**.*

Will the day soon dawn when it will be conclusively shown that the Wessely School have spent their careers in a *"null field"* in relation to their efforts to designate ME/CFS as a behavioural disorder?

<u>Apparent misrepresentation in the PACE Trial?</u>

The related issues of apparent coercion, misrepresentation and informed consent in relation to the MRC PACE Trial deserve close attention.

Hawkins and Emanuel (Hastings Centre Report 2005:35:5) are clear: "*if the potential subject is competent to give informed consent, three requirements must be satisfied: **there must be full disclosure**, the subject must understand what is disclosed, and the subject must consent voluntarily…Consent may be invalid ….(if) the disclosure was inadequate…**When disclosure is intentionally absent or inadequate, we have a case of deception**".*

Any failure to make "***full disclosure***" is a material concern in a clinical trial and it seems that PACE Trial participants were not informed about key issues, including the following:

1. The Investigators believe "CFS/ME" to be a behavioural disorder and consequently failed to take account of the extant literature, which is a very serious issue in a clinical trial.

It is not credible to think that the PACE Trial Investigators are or were unaware of the considerable body of international evidence about the nature of the disorder in which they profess to be experts, or about the evidence showing that CBT is not an effective treatment for ME/CFS; indeed, Simon Wessely is on record numerous times saying so (see "Conflicting information" above).

It must not be overlooked that one of the Principal Investigators, Professor Trudie Chalder, is on record as asserting that "CFS" is a "*classical psychosomatic*" disorder described as "*a psychiatric illness with marked physical symptoms*" (see Section 1 above), **but this belief was withheld from participants involved in the PACE Trial**. If full disclosure had been made to potential participants, it is unlikely that they would have agreed to take part in the PACE Trial.

What is so striking is that participants are not only having this necessary information withheld from them but, via the Manuals, they seem to be being repeatedly misinformed about the nature of ME/CFS and about the efficacy of CBT/GET (see Section 4 below). This immediately reduces their autonomy and their choice.

The empirical evidence is that, far from being "somatisers", the vast majority of people with ME/CFS are quietly courageous and adjust astonishingly well to the huge disability they face, especially given the degree of medical disinterest, denigration and social isolation. Such adjustment should be seen as a triumph of strength, not as maladaptive behaviour as the Wessely School assert.

2. To inform therapists but not participants that CBT and GET work on the premise of there being no pathology in "CFS/ME" (placating participants by telling them that there are "physiological" disturbances, which the PIs in reality believe to be due to deconditioning) seems not only to misrepresent the facts about ME/CFS (because, as illustrated in Section 2 above, there is abundant evidence of underlying pathology in ME/CFS) but, according to Professor Paul Cheney, may even potentially endanger the life of any participant with true ME who may have serious and significant cardiovascular dysfunction.

According to Miller et al, deception of research participants is incompatible with informed consent and clearly conflicts with the ethical norms governing clinical research. It violates the principle of respect for patients by infringing their right to choose whether or not to take part in the research that must be based on full disclosure of all relevant information (FG Miller et al. PloS Medicine 2005:2:9:0853-0859).

Patients expect to be able to trust in, and to receive comprehensively truthful communications from, clinicians and clinical investigators, but in the case of the PACE Trial, participants were not told that the Trial was predicated on the assumption that they do not have a physical disease, which many people regard as deceiving participants.

Miller et al argue that clinician investigators who deceive patients in the course of research are acting fraudulently (FG Miller et al. PloS Medicine 2005:2:9:0853-0859).

On page 28 of the therapists' CBT Manual in the table "Distinguishing Between APT, CBT and GET" it states that CBT and GET do not – as noted above in this section -- work from a pathological assumption. This is a clear statement from the Wessely School that they do not believe ME/CFS patients have a physical illness, yet the Manuals train therapists to let participants think that they <u>do</u> accept it as a physical illness. Therapists are explicitly told to use "biomedical language" and are warned not to challenge patients who

say that they have physical symptoms, but the clear message to therapists is that such symptoms are simply "perceptions". The therapists thus seem to be operating from a platform of pretence.

The therapists' manual on GET says (page 24): "*The more severely disabled group of CFS/ME patients were excluded from previous studies as the studies involved an exercise test that may have been too challenging.* ***However due to greater levels of inactivity in the more severely disabled group, the deconditioning model should apply equally if not more to these patients***", but in the participants' material, certain words like "deconditioning" are either absent or downplayed, yet in the therapists' Manuals, "deconditioning" is at the heart of the programme and is used throughout.

Such lack of openness in the patients' material does seem to be misrepresentation. The Wessely School's "deconditioning" model of "CFS/ME" is not evidence-based, let alone proven (indeed, it has been disproven numerous times – see for example Twisk and Maes, Neuroendocrinol Lett 2009:30(3):284-299), and it contrasts with the biomedical model of ME/CFS that is supported by a respected literature of solid scientific evidence.

3. The known adverse effects of the interventions used in the PACE Trial, especially GET (see Section 1 above), appear to have been down-played by the Principal Investigators.

4. The assumptions of the Principal Investigators (ie. that there is no physical disease process) are frequently stated as fact (see Section 4 below for actual quotations from the Manuals).

5. Sections 3 and 4 of this Report contain illustrations of what appear to be misrepresentation in the PACE Trial literature: for example, in the PACE Trial Newsletter Issue 2 there is a "recruitment graph" purporting to show actual recruitment compared with target recruitment and the two lines matched almost exactly (ie. the projected recruitment was almost exactly the same as actual recruitment). From the documents obtained under the FOIA, given that there were significant recruitment problems, this seemed improbable. The text under the graph states: "*All six hospital centres combined have not only managed to meet the revised recruitment targets, but also to exceed them. This is a fantastic achievement for the trial team"*. The important word in the text is the word "*revised"* (ie. it shows actual recruitment versus "revised" target recruitment). Unless patients (who may have been cognitively impaired) were paying close attention, this conveys the message that the Investigators had no difficulties in finding participants and creates the (erroneous) impression that people were flocking through the doors, which was not the case.

6. The Investigators' hypothesis that is being tested in the PACE Trial (ie. that CBT and GET are effective treatments for "CFS/ME" but that APT is not an effective intervention) is assumed by the Investigators (and hence by the therapists) to have been proven, with therapists informing participants via the Manuals that <u>they can expect to recover with CBT and GET</u>, but not with APT, which not only seems to be in breach of the GMC regulations (Good Medical Practice 2006 – see below) but seems to show that the Principal Investigators may have been inaccurate and may also have biased the trial from the outset by the way information was presented to participants in a way that would favour the PIs' desired outcome.

This is a serious concern, because participants in the CBT and GET arms of the trial were effectively being told that "we already know the treatment you are to receive is effective and safe", but those in the APT arm of the trial were not given such reassurance. To give an unfair advantage to two arms of the trial by (a) engaging the placebo response and (b) putting subtle pressure on participants to <u>report</u> feeling better even if they did not feel better (because people want to please their therapists and may blame themselves if the therapy does not work) is introducing an unacceptable bias into an MRC trial. Many people believe it expedient of the Investigators to have withheld from PACE Trial Participants the fact that two of the Principal Investigators withdrew from the Chief Medical Officer's Working Group on CFS because they did not agree with pacing, yet in the PACE Trial those same people are now claiming that CBT, GET and APT are <u>all</u> forms of "pacing".

7. The competing interests of the Investigators were not brought to the attention of participants, especially the Investigators' close association with the DWP and the medical and permanent health insurance industry.

8. Potential participants were assured that they would be receiving "*specialist medical care*" ("SSMC"), which implies that participation in the PACE Trial would afford them specialist medical care **that is not available elsewhere.** According to Hawkins and Emanuel (Hastings Centre Report 2005:35:5): "*Concern may arise if the subject believes falsely that she will receive more personal medical benefit than is possible under the circumstances*".

The PACE Trial Protocol (version 5.0) states on page 57 that the Investigators expect 10% of participants receiving "SSMC" (Standardised Specialist Medical Care) to improve versus 60% receiving CBT. **Quite apart from the fact that it is expected that one group will do six times better than another group (if it is already known that an intervention is effective, why obtain money to carry out such a trial?), calling one arm of the trial "SSMC" seems inaccurate because, as noted above, it gives the impression that participants will be receiving specialist medical care (ie. the best medical care available), which clearly is not the case as "SSMC" consists of doing nothing at all apart from a CFS Clinic doctor giving general advice about balancing activity and rest.**

The published (abridged) Protocol for the PACE Trial defines"SSMC" thus: "***SSMC will include visits to the clinic doctor with general, but not specific, advice regarding activity and rest management***" (BMC Neurology: 8th March 2007:7:6). **To mislead participants by asserting that such "*general, but not specific, advice*" constitutes "*Specialist Medical Care*" seems unacceptable.**

As de Melo-Martin and Ho make plain (Journal of Medical Ethics 2008:34:202-205), if subjects incorrectly attribute a primarily therapeutic intent to research procedures, they are likely to underestimate risks or overestimate benefits. Such misplaced trust presents serious ethical problems, one of which being that participants often enrol in clinical trials based on their physicians' recommendations, so a realisation of misplaced trust in researchers may also lead patients to question the competence of their own physician and to lose trust in them also. Mindful of Professor White's proposed letter of advertisement of 14th July 2006 asking GPs to send anyone who suffered from "*chronic fatigue (or a synonym)*" to a PACE Trial Centre (see Section 3 above), this is a significant issue. As de Melo-Martin and Ho note, if participants cannot trust researchers and Ethics Committees to be attentive and vigilant in upholding the highest level of integrity, this cannot be of benefit to anyone.

The issue of misrepresentation in the PACE Trial is a material concern. It seems irrefutable from the content of the various Manuals that the level of such misrepresentation to which participants have been exposed is disturbing (see Section 4 below).

In their decisive paper "When is deception in research ethical?" (Clinical Ethics 2009:4:44-49) Athanassoulis and Wilson state: *"One of a Research Ethics Committee's main tasks is to ensure that potential research participants are in a position to give valid consent.* ***Research participants cannot give consent without adequate information…If some relevant information is not communicated…this is not because of a mistake or incompetence, but rather because the information is withheld intentionally".***

The authors draw distinction between intentionally giving false information and withholding information (the former of which is always deceptive). In the MRC PACE Trial, the intention seems to be that participants will form a false belief about the nature of ME/CFS and will adopt the Wessely School's belief. Athanassoulis and Wilson argue convincingly that: ***"intentionally causing someone to hold a false belief is a sufficient condition for deception"***.

They refer to a case used in training days for Research Ethics Committees (Research Ethics Committees are trained by the Department of Health, the primary job of an ethics committee being to determine whether a research project is suitable for participants to be invited to take part in it) that was turned down **on the grounds that it deceived the subjects as to the true nature of the trial** and they conclude that: ***"Valid***

consent requires that the participant be given information adequate to making a reasonable decision as to whether to take part in the research or not. Where the information is less than all that is relevant, then the participant does not have adequate control of the risk", failure of which will in general ***"be prima facie ethically unacceptable".***

Whilst not specifically related to ME or the MRC PACE Trial, an article in the Guardian on 18th September 2009 by Sarah Bosely on "*dubious research practices*" quotes Jane O'Brien, Head of Standards and Ethics at the General Medical Council (GMC) as saying that the GMC disapproves of misleading people about the credibility of research. The article says: "(Jane O'Brien) *added that* ***the GMC felt it important to play a role in ensuring good conduct in research****. About a year ago, she said, they took soundings of bodies that regulate and support research, such as the Medical Research Council, asking whether the GMC should be involved. 'The response was yes, because we are the people who can strike doctors off in the end' ".*

In the light of such confirmation, the GMC may be asked to investigate the PACE Trial, since "good conduct in research" seems to be singularly lacking in this particular MRC trial.

The MRC Good Research Practice (second edition, September 2005) recommends on page 2 that the 1995 Nolan Committee on Standards in Public Life that requires adherence to seven principles (selflessness, integrity, objectivity, accountability, openness, honesty and leadership) provides a good starting point. It seems that the MRC PACE Trial Investigators may have failed on several of those counts.

Furthermore, given that clinicians had to be tempted by financial rewards to refer patients into the PACE and FINE Trials (see Section 3 above), it may be postulated that the trials are of concern on that count also. It is the case that the companion FINE Trial Patient Information Sheet assures patients that *"Your GP is not being paid for his or her participation in this trial"*, but there is a different message for GPs, because the GP invitation letter states: *"(GP) Practices will be recompensed by the Department of Health for time spent in identifying and recruiting patients (£26.27 per referral)"*. This would seem to be an example of outright misrepresentation regarding these trials.

9. So that participants should not think that the therapists believe "CFS/ME" to be a behavioural disorder, CBT and GET are portrayed in the PACE Trial literature as successful "treatments" that have been used effectively in other "physical" diseases such as cancer. That this is untrue in relation to cancer has been confirmed in writing by a major UK cancer charity (Cancer Research UK) on 6th December 2008 (personal communication).

Furthermore, at the 2008 British Psychological Society meeting in Dublin, during the oncology session it was confirmed that only about one in ten people with cancer are offered CBT, and then only if they are distressed and really struggling to adjust. Importantly, **CBT is offered only after all biomedical testing has been completed and the diagnosis confirmed.** Offering CBT before then was shown to be counterproductive and unhelpful, yet this is exactly what is happening in ME/CFS.

It is notable that in October 2009 Dutch psychologists reported that in relation to cancer patients undergoing chemotherapy: *"the suggestion that physical exercise reduces fatigue is not proven"*. They further pointed out that: "*In the past, several studies have refuted the hypothesis that improving physical condition, or increasing physical activity, leads to a reduction in fatigue. In fact, the two exercise studies in breast cancer patients cited by Adamson et al (2009) observed…no improvement in fatigue"* (http://www.bmj.com/cgi/eletters/339/oct13_1/b3410#224003).

10. The special interest of the DWP in the PACE Trial was not made sufficiently clear to participants (ie. the importance of the PACE Trial to the DWP was not mentioned, nor the fact that this is the only clinical trial that the DWP has ever funded, information that potential participants entering a "clinical" trial might have wished to be aware).

Socio-economic data was to be collected even before a participant was carefully chosen by the Wessely School: the Protocol states:

"Where the patient is thought to be suitable by the clinic doctor…and the patient agrees to be assessed for eligibility, the clinic doctor will forward the patient's contact details to the RN (research nurse). The RN will contact the patient to arrange the first research visit".

If only the patients who were "*thought to be suitable*" by the clinic doctor for inclusion in the "randomised" MRC PACE Trial were chosen, this would seem to introduce a source of possible bias, because it is only if the Wessely School clinic doctors deemed the patient to be eligible that patients were told about the Trial by the clinic doctor (yet the original intention was to recruit consecutive new patients at the CFS Clinics, which was subsequently amended to include patients who had previously undertaken a programme of CBT).

The next pre-trial assessment was at Baseline Visit 1, which set out to collect personal data that seems to have little bearing on a clinical trial but could be of value to the DWP and the permanent health insurance industry.

The collected data included not only the customary demographic details, date of birth, age, sex, ethnicity, marital or partner status, years of education, occupation (the latter would obviously afford information about a participant's earnings) but also current and specific membership of a self-help group.

"*After visit 1 the research nurse will discuss the patient's potential eligibility with the centre leader"*, so once again it was only if the potential participant's data was deemed suitable for the Wessely School's purposes that the patient was allowed to enter the Trial. Was this true randomisation as participants were led to believe (**P**acing, **A**ctivity, and **C**ognitive behavioural therapy, a randomised **E**valuation)?

Participants selected in this way may not be deemed to be a representative patient cohort and the data generated should thus only be extrapolated to an identically-selected population, which could nullify the PACE Trial Investigators' claim that the trial is "randomised".

In October 2002 The Lancet's Department of Ethics published a report setting out guidelines to protect participants in clinical trials; key points are:

"*Clinical reports typically include a statement that the research protocol was approved by an ethics review committee, and that informed consent was obtained from participants.*

"Studies that have morally controversial features, such as….deception, might be dismissed as unethical unless the rationale for including such features and details of safeguards to protect research participants from…exploitation are explained.

"Studies in which participants are deceived should discuss why such a measure was deemed necessary, and how informed consent was obtained.

"One could argue that there is no need to burden researchers with the task of describing ethical matters, provided that studies have received previous review and approval by an ethics committee" (FG Miller et al. Lancet 2002:360:1326-1328).

It is easy for researchers to side-step ethical issues by ascribing responsibility to an ethics committee, but in the case of the MRC PACE Trial, it seems that the West Midlands MREC did not have the necessary grasp of the issues involved; the question therefore arises as to why this was so and why they commended Peter White on the trial's design when it seemingly did not conform to even elementary rules of procedure.

If in the PACE Trial the Wessely School are assessing patients with chronic "fatigue", then they cannot without misrepresentation refer -- as they do -- to those patients as suffering from "ME" – those who do not have ME should not be included in a trial that purports to be studying those who do have ME, and those who do have ME should not be subjected to incremental aerobic exercise. To claim that the MRC PACE Trial is studying patients with ICD-10 G93.3 ME/CFS would seem to be misleading.

The international medical and scientific literature is replete with evidence of the need to distinguish between ME/CFS and "CFS/ME" or "chronic fatigue".

Referring to those psychiatrists who conflate "chronic fatigue" with "chronic fatigue syndrome", one US physician with over a decade of experience of ME/CFS observed:

"They often fail to distinguish between 'chronic fatigue' and 'chronic fatigue syndrome'. The former is a fairly common symptom in medical clinics that does have a high linkage to already-present psychological problems. The latter is a specific medical condition. Their sloppiness has led to all kinds of trouble and misunderstandings" (http://www.prohealth.com//library/showarticle.cfm?libid=8142 23rd January 2002).
In 2000 Anthony Komaroff, Professor of Medicine at Harvard and a world leader in ME/CFS, summarised the key areas in which ME/CFS differs from psychiatric illness in The American Journal of Medicine:

"Objective biological abnormalities have been found significantly more often in patients with (ME/CFS) than in the comparison groups. ***The evidence indicates pathology of the central nervous system and immune system. Autonomic nervous system testing has revealed abnormalities of the sympathetic and parasympathetic systems that are not explained by depression or physical deconditioning. Studies of hypothalamic and pituitary function have revealed neuroendocrine abnormalities not seen in healthy control subjects. There is considerable evidence of a state of chronic immune activation. In summary, there is now considerable evidence of an underlying biological process which is inconsistent with the hypothesis that (ME/CFS) involves symptoms that are only imagined or amplified because of underlying psychiatric distress. It is time to put that hypothesis to rest****".* (The Biology of the Chronic Fatigue Syndrome. Am J Med 2000:108:99-105).

Failure by the Wessely School to acknowledge the existence of the cardinal symptoms of ME/CFS means that, despite their insistence to the contrary, they cannot be studying patients with ME/CFS.

It seems improper for the Trial Investigators to deny the existence and nature of these symptoms by refusing to allow patients with such symptomatology to be included in the PACE Trial that purports to be studying the disorder in which those symptoms occur.

Other examples of apparent misrepresentation include the following:

11. According to the PACE Trial literature, doctors "know" that most illnesses have a number of causes and that this is *"probably"* true for "CFS/ME":

"This means doctors prefer not to talk of causes. They use the more accurate term 'factors' and they divide up factors into three types:

- *Factors that make someone more likely to get the illness. Doctors call this a PREDISPOSITION*
- *Factors that bring on the illness in the first place. Doctors call this a TRIGGER*
- *Factors that stop people recovering from the illness. Doctors call this a MAINTAINING factor".*

Participants are thus not only being patronised but are being told by NHS personnel that, by the same principle, it is usual for doctors to talk about predisposition, triggers and maintaining factors in <u>all</u> diseases,

which must mean, for example, in relation to stomach ulcers (which invalidates the work of the 2005 Nobel prize-winners Marshall and Warren who discovered *H. pylori*) and in relation to cancer and to motor neurone disease, when this is patently untrue.

12. The authors of the Trial information are adamant: *"There is no strong evidence that infections are maintaining factors in CFS/ME"*, a statement that is readily disproved by reference to the literature and is therefore misleading.

13. Even more astonishingly (given the enormous volume of immunological papers showing serious disruption of the immune system in ME/CFS patients), the Trial information informs participants that: *"**Minor** abnormalities of the immune system are commonly found in people with CFS/ME"* (the implication being that deconditioning is known to affect the immune system but that any "minor" immune dysfunction is reversible with CBT and GET). This should be compared with how Nancy Klimas, Professor of Medicine, University of Miami School of Medicine, Director of Immunology and Director of AIDS Research, and world-renowned expert on ME/CFS, described the documented immune abnormalities **18 years ago** (quoted in Section 2 above but repeated because of its importance):

"*The NK (natural killer) cell is a very critical cell in (ME)CFS because it is clearly negatively impacted.* ***The most compelling finding was that the NK cell cytotoxicity in (ME)CFS was as low as we have ever seen it in any disease****. This is very, very significant data. In (ME)CFS the actual function was very, very low --- 9% cytotoxicity: the mean for the controls was 25, in early HIV and even well into ARC (AIDS related complex, which often precedes the fully developed condition), NK cytotoxicity might be around 13 or 14 percent****. (ME)CFS patients represent the lowest cytotoxicity of all populations we've studied"*** (Immunological Markers in (ME)CFS. The CFIDS Association Research Conference, November 1990, Charlotte, North Carolina. Reported in CFIDS Chronicle, Spring 1991; pp 47-50)

Attention must be drawn to Klimas' research 18 years later published in BMC Medical Genomics: 2009:12: (http://www.biomedcentral.com/1755-8794/2/12), which exposed Gulf War Illness patients and matched controls to an exercise challenge to explore differences in immune cell function measured by classic immune assays and gene expression profiling. The study is relevant to the MRC PACE Trial because the authors state: "*The symptom spectrum of (GWI) is similar to (ME)CFS".* The study measured peripheral blood cell numbers, NK cytotoxicy, cytokines and levels of 20,000 genes immediately before, immediately after and after four hours following a standard bicycle ergometer exercise challenge.

"GWI patients demonstrated impaired immune function as demonstrated by decreased NK cytotoxicity and altered gene expression associated with NK cells function. Pro-inflammatory cytokines, T-cell ratios, and dysregulated mediators of the stress response (including salivary cortisol) were also altered in cases compared to control subjects.

"An interesting and potentially important observation was that the exercise challenge augments these differences, with the most significant effects observed immediately after the stressor. This… provides a paradigm for exploration of the immuno-physiological mechanisms that are operating in GWI and similar complex syndromes (such as ME/CFS).

"Our results mirror what is seen in the literature with regard to (ME)CFS: chronic immune activation, low cytotoxic immune function, and dysregulated mediators of the stress response with low baseline salivary cortisol, strongly reflecting the overlap between these two syndromes. Decreased functional capacity of NK cells is the one consistent finding in (ME)CFS and Siegel et al demonstrated that low NK cell function defined a more severely ill cohort.

*"**Our data confirmed reports that the NK cell subsets are more sensitive to exercise stress than any other cell subtypes.***

"Enhanced negative-feedback sensitivity to glucocorticoids is often seen in (ME)CFS, as well as blunted adrenocorticotropin response to stressors, and hypocortisolism. This supports the hypothesis that hypo-function of the HPA axis plays a role in (ME)CFS, and probably in GWI also. Disturbances of the HPA axis can be considered as a pathway that links to the immunological disturbances evidenced in (ME)CFS and GWI.

"The shift in immune system functioning towards a Th2 (or allergy) profile has been evidenced before in GWI and (ME)CFS patients.

"Several conditions are associated with changes in stress system activity through modulation of inflammatory responses and the Th1/Th2 balance they may suppress or potentiate disease activity and/or progression (sic). *The differences seen here in stress hormones may represent an important mechanism by which stress affects immune-related disease susceptibility, activity and outcome.*

"This study shows that exercise induces considerable physiological change in the immune system.

"The differences we found are focused in the NK and T-cell populations, involving signal transduction processes.

"The question arises whether the altered number of NK cells is a consequence of the pathological status or a primary condition that leads into the disease.

"*Another important question is what role do NK cells have in maintaining immune homeostatis in disorders…such as (ME)CFS and GWI?* ***Our data support the idea of chronic immune cell dysfunction, which appears to be centred on the NK and T-cell lymphocyte populations.***

*"**The most significant differences were observed immediately after the exercise challenge. This has positive implications for the development of laboratory diagnostic tests for this and other syndromes such as (ME)CFS".***

So extensive is the knowledge of the disrupted immune system in ME/CFS that for the PACE Trial Investigators to dismiss it as "*minor abnormalities*" and to misinform participants seems culpable.

14. Participants who asked for references that support CBT and GET or who ventured to mention the information on the internet that does not support the Wessely School's notions were to be instructed that there is a significant amount of inaccurate information on the internet and in other publications, and that it should be approached with caution. This seems intentional, as there is plenty of information on the internet provided by the Wessely School themselves showing that CBT/GET does not work in "CFS/ME" which, if participants were aware of it, would undermine the Investigators' attempts to conceal it

15. The therapists' CBT Manual seems to amount to a systematic, highly detailed description of how to indoctrinate someone. It has been described by a scientist who has read it in its entirety as *"a really sinister document"* (personal communication).

All the therapists' Manuals train therapists how to deal with people who think there is something physically wrong with them: therapists are to tell patients that they agree with them, but as noted above, in truth the therapists are trained to believe that apart from deconditioning there is nothing physically wrong with the participants at all so, essentially, it appears that therapists are misleading patients.

There is no evidence that people with ME/CFS have any kind of psychiatric diagnosis, yet in the PACE Trial participants are being patronised as though they are mentally incompetent. Information is withheld from them and their symptoms are ignored or dismissed, whilst at the very heart of the intervention is the assumption (which participants must be persuaded to accept) that their thoughts, beliefs and appropriate behaviour are wrong. What other contemporary MRC clinical trial has treated participants with such apparent disdain and such fundamental disregard for their autonomy?

16. As noted above, therapists and research nurses are constantly urged that in order to improve compliance, they should show warmth and empathy towards participants, which seems to border on dishonesty because it is insincere. The objective appears to be to ensure that the participants are doing the therapists' bidding.

Therapists are trained to say to participants, for example, words to the effect of: "You may have had bad experiences before, but we know you're really ill and are on your side"; this seems duplicitous and fundamentally misleading because it is not genuine.

This emphasis on false warmth pervades these Manuals and is believed by many to be reprehensible: it has overtones of the Stockholm syndrome, in that the motive seems to be deliberately to induce an emotional attachment to the therapist who is exhibiting such warmth and empathy so that the participants will want to trust and please the therapist.

Throughout the Manuals, the emphasis seems to be on how to accomplish indoctrination of the Wessely School's beliefs about "CFS/ME".

It seems that therapists are instructed to mislead people either directly or indirectly, which seems to mean that those responsible for the PACE Trial have instructed NHS personnel to misinform sick people. Can this be ethical?

For example, page 125 of the Participants' CBT Manual (information for relatives) states: "*It is important to stress that any increase of symptoms is both a normal and temporary side effect that occurs because they are doing more".*

This is another assumption stated as fact, but this is the very hypothesis that the PACE Trial is testing, not a proven fact, so is it not misleading to state it as fact?

Assumptions stated as fact in the Manuals need to be addressed because they show that:

- the PACE Trial Investigators and therapists seem to have no understanding of the scientific process
- they seem to be misinforming patients and relatives which, if so, is unethical.

If information is withheld and patients and relatives are misinformed, choice becomes reduced, thereby enhancing the control afforded to and exerted by the therapist and ultimately by the Wessely School, the State and the the multi-national corporations that now dominate and control medical and research institutions and whose life-blood is profit (Politics isn't working. *Channel 4, 13th May 2001).* **In their portrayal of ME/CFS as a mental illness, Wessely School psychiatrists and their colleagues are misleading PACE trial participants and therapists alike.**

The abundance of misrepresentation about ME/CFS shows that the MRC and DWP are funding research based on the belief that "CFS/ME" (which the PACE Trial Investigators insist is the same as ME/CFS) is a mental health problem, when to do so is deemed by many to be unethical. It seems that no amount of scientific evidence will influence the Wessely School's beliefs about "CFS/ME", or their on-going intention to re-classify it as a mental disorder.

For example, in 2003, Simon Wessely asserted that neither he nor his group had any intention of reclassifying ME/CFS as a mental disorder (despite the Institute of Psychiatry – using Wessely's own material -- having attempted to do so in 2000 by including it in the Guide to Mental Health in Primary Care):

"Probably nearly all (GPs) accept that there are important psychological and social issues surrounding CFS. The question of classification and the WHO is a storm in a teacup. There is no desire to see CFS as an exclusively mental

health problem. There is no desire to change the current status quo. Where do we at King's stand on this issue? The answer is simple. We are perfectly happy with the status quo. There is no pressure from here or anywhere else to alter the current definitions. As practitioners we are aware that CFS/ME is an umbrella term, under which we see a wide range of disability" (What's in a name? December 10, 2003: http://tinyurl.com/l8zktz).

This must be compared with the PACE Trial information, which clearly states: "*Medical authorities* (meaning the Wessely School) *have decided to treat CFS and ME as if they are one illness".*

Despite Wessely's public assertion that he and his group are "*perfectly happy with the status quo*" **(the *status quo* is that ME/CFS is formally classified as a neurological disorder)**, in October 2008, Cambridge University Press published the fourth edition of "Essential Psychiatry" co-edited by Simon Wessely. Chapter 23 ("General Hospital Psychiatry") is co-authored by Professors Matthew Hotopf and Simon Wessely and includes a section on "medically unexplained symptoms". It is replete with self-references.

Despite the large body of scientific evidence about ME/CFS, Wessely remains intransigent, asserting categorically that chronic fatigue syndrome is a functional somatic syndrome (ie. a mental disorder) and that the aim of CBT is "*to help change beliefs about the illness as well as associated behaviours"* and that "***social factors which may be important in maintaining unexplained symptoms include systems of state benefit or private insurance in which the sufferer is forced to maintain a sick role to continue to receive compensation".*** He says: "*Cognitive-behavioural formulations of unexplained syndromes such as chronic fatigue syndrome suggest that (deconditioning) is one factor that maintains disability, perhaps by a vicious circle of avoidance, deconditioning, catastrophic interpretations of symptomatology and hence further avoidance".*

Wessely seemingly refuses to accept the documented biological abnormalities known to exist in ME/CFS as causal, preferring to believe that: *"such changes are as a result of behavioural changes related to the disorder, such as reduced activity and sleep disturbance, rather than a primary cause".*

No matter what pathology is demonstrated in ME/CFS, Wessely often seems to rush to replicate it but almost invariably fails to do so, thus allegedly substantiating his own belief about the nature of the disorder. The most recent example is the paper he co-authored with Otto Erlwein and Professor Myra McClure et al (Failure to Detect the Novel Retrovirus XMRV in Chronic Fatigue Syndrome. PloS One, 6th January 2010:5:1:e8519), in which he declared no competing interests. The paper concluded: "*Based on our molecular data, we do not share the conviction that XMRV may be a contributory factor in the pathogenesis of CFS, at least in the UK".*

However, as the CFIDS Association of America pointed out: "*The new report…failed to detect XMRV in CFS, but should not be considered a valid attempt to replicate the findings described by Lombardi et al in the October 8th 2009 Science article"* (Co-Cure Res: 5th January 2010).

Not only did the Wessely et al study not use the same entry criteria as Lombardi and Mikovits et al (who used both the 1994 Fukuda CDC definition and the Canadian case definition – which the Wessely School reject), but the scientific director of the CFIDS Association, Dr Suzanne Vernon, provided evidence why the Wessely et al study should not be considered a valid attempt to replicate the Lombardi and Mikovits study:

"Both studies included CFS patients defined by the 1994 (Fukuda CDC) *case definition criteria, but this is where the comparability ends. Here are some of the ways the PloS ONE and Science methods differ:*

- *The blood was collected from CFS patients in different types of blood collection tubes*
- *The genomic DNA was extracted and purified using different techniques*
- *The amount of genomic DNA included in the amplification assay was different*
- *Different primer sequences were used that amplified different regions of the XMRV proviral DNA*
- *The conditions of the PCR amplification assay were different – from the numbers of cycles, to the type of polymerase used.*

"These variances in procedure could make the difference between detecting XMRV or not" (http://www.cfids.org/cfidslink/2010/010603.asp).

An official statement issued on 6th January 2010 by Frankie Vigil of R&R Parters for the Whittemore Peterson Institute was robust about the Wessely et al study:

"*This study did not duplicate the rigorous scientific techniques used by WPI, the National Cancer Institute and the Cleveland Clinic, therefore it cannot be considered a replication study nor can the results claim to be meaningful results.*

"The WPI study was published after six months of rigorous review and independent laboratory confirmations, proving that contamination had not taken place….In contrast, this latest study was published online after only three days of review (and) patient samples used in the UK study…may have been confused with fatigued psychiatric patients, since the UK has relegated "CFS" patients to psychiatric care and not traditional medical practices" (Co-Cure NOT 6th January 2010).

Wessely, however, apparently remains unconvinced that the retrovirus XMRV has anything to do with ME/CFS and seems relieved that the samples he provided from his own cohort of patients were found to be negative, saying that the Lombardi / Mikovits study: "*if confirmed, would have a serious impact on understanding the pathogenesis of this complex and debilitating disease and its treatment".*

Wessely School psychiatrists readily accuse patients with ME/CFS of "catastrophising" their symptoms, and of holding "catastrophic illness beliefs", but their studies do not address the physical symptoms of ME/CFS other than "fatigue", classic symptoms such as repeated, prolonged vertigo (which is catastrophic), or frequent episodes of incapacitating chest pain of similar intensity to a myocardial infarction (which are catastrophic), or the inability to look after oneself (which again is catastrophic). All these are documented in the ME/CFS literature, but Wessely School psychiatrists exclude such patients from their studies, yet claim that they are studying people with "CFS/**ME**". Moreover, a recent study found no evidence of catastrophising in (ME)CFS, and that altered pain thresholds cannot be attributed to catastrophising (Meeus M et al; Clin Rheumatol January 2010; Epub ahead of print).

The many misrepresentations perpetrated on participants in the PACE Trial appear to fall well below standards of basic decency because they deny current knowledge.

There is no evidence that misrepresentations about ME/CFS by the Wessely School are about to cease.

In December 2008, the Chief PACE Trial Investigator, Peter White, gave a presentation at a Neurology and Psychiatry Teaching weekend organised by the British Neuropsychiatry Association (BNA) 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 can be accessed at http://bnpa.org.uk/doc/HANDBOOK.pdf.

Extracts from the Handbook show that White apparently remains unmoved by biomedical science and by the taxonomic rules governing the WHO ICD classification:

"***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/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**.

The Handbook continues:

"Maintaining or perpetuating risk markers are most important in determining treatment programmes, since reversing of maintaining factors should lead to improvement. Reasonably well established factors include mood disorders, such as dysthymia, illness beliefs such as believing the whole condition is physical, pervasive inactivity, avoidant coping, membership of a patient support group, and being in receipt of or dispute about financial benefits.

"Few pathophysiological findings in CFS have been replicated in independent studies".

It should be noted that White cites Wessely's 2003 paper (A systematic review and critical evaluation of the immunology of chronic fatigue syndrome: J Psychosom Res 2003:55:2:79-90) in which Wessely referred to "*the sheer number of papers"* but then – seemingly failing to acknowledge that just such criticisms have been levelled at his own work -- asserted that *"non-systematic general reviews in the field of CFS are associated with bias, influenced by professional affiliations"* and asserting that any association between CFS and low NK cells may be "*erroneous. ..There was an inverse association between study quality and finding low levels of natural killer cells, suggesting that the association may be related to study methodology….* ***The conclusions of this systematic review differ from a recent traditional narrative of the immunology of CFS. No consistent pattern of immunological abnormalities is identified".***

This seems to show that despite the abundance of immunological papers published since 1996 when he gave similar advice in the Joint Royal College's Report, Wessely persists in his long-held belief that immunological abnormalities are of no significance: "*Some use the results of immunological tests as evidence for a so-called 'organic' component in CFS…Such abnormalities should not deflect the clinician away from the biopsychosocial approach…and should not focus attention solely towards a search for an 'organic' cause"* (Chronic Fatigue Syndrome. Joint Royal Colleges' Report CR54, RCP, October 1996).

White's BNA presentation continued: *"Those (findings that have been replicated) include…physical deconditioning, and discrepant reports between perception of symptoms and disability and their objective tests.*

"The discrepancy between subjective states and objective tests…may be related to enhanced interoception (the perception of visceral phenomena)…One hypothesis currently being tested is that the predisposition to functional somatic syndromes is caused by enhanced interoception. Recent work suggests that these factors may be reversed by rehabilitation.

"The essence of specialist care is rehabilitation…The two approaches with the greatest evidence of efficacy are CBT and GET. *Approximately 60% of patients report significant improvement with these approaches and* ***about 25% report full recovery, which lasts"*** (an assertion that is disputed by many).

(Attention is drawn to the Statement for the High Court of immunologists Professors Nancy Klimas and Mary Ann Fletcher referred to above, who voiced their scepticism about Peter White's claim of 25% recovery: *"Dr Peter White of the UK presented his work using behavioural modification and graded exercise. He reported a recovery rate of about 25%, a figure much higher than seen in US studies in (ME)CFS and, even if possible, simply not hopeful enough to the 75% who fail to recover"*).

Peter White continued: "*Is CFS neurological or psychological? This is a nonsensical question".*

White's attempt to overcome Cartesian dualism may be thought to justify the stance of the Wessely School, but it may well be thought that it is the work of the Wessely School that has done so much to perpetuate the stigma of a mental health label, with the consequent denial or removal of benefits for those with ME/CFS.

At the press release to launch the joint Royal Colleges' 1996 report, Dr Robert Kendell, then President of the Royal College of Psychiatrists, was quoted as saying "*To try to distinguish between a physical illness and a psychological illness is not just wrong, it's meaningless*" (Press Launch, Royal College of Physicians, London, 2nd October 1996); this fallacy was encapsulated in a letter to the Guardian newspaper which said: "*Try telling that to someone with terminal cancer*" (Letter: H.J.H.Berger, Guardian, 5th October 1996, page 16).

White's BNA presentation continued: *"Fatigue …should be differentiated from fatiguability. Fatiguability…is commonly reported with neurological diseases such as multiple sclerosis and myopathies"*. Ironically, White seems unaware that the Wessely School's 1991 Oxford criteria (with which he was involved, not least as a financial sponsor) specifically exclude this cardinal symptom of ME/CFS from their case definition of "CFS", thereby rendering it scientifically meaningless for them to claim that ME is included in their Oxford case definition.

The unwarranted influence of this group of activist psychiatrists is a grave matter; they are often funded by the taxpayer as well as by charities such as the Linbury Trust, which has funded the Wessely School's studies of "chronic fatigue" since 1991.

The Linbury Trust is one of the Sainsbury supermarket family trusts: by 2003 David Sainsbury had donated over £11 million to the UK Labour Party and in the Blair New Labour Government he was promoted to the House of Lords (he is now Lord Sainsbury of Turville) and became Minister for Science. As such, he was responsible for the Office of Science and Technology as well as for the chemical and biotechnology industries, and for the Research Councils, including the Medical Research Council.

The Office of Science and Technology monitors all government funding of research grants and controls official science policy, and it is "policy" which determines the research to be funded: on 11th May 2000, the Secretary of State for Health (Yvette Cooper MP) confirmed ***"The Department funds research to support policy"*** (Hansard, 11th May 2000:461W 462W).

On 22nd June 2005 Laurie Taylor presented a programme called "Thinking Allowed" on BBC Radio 4, one of a series of programmes in which contributors discuss topical items coming out of the academic and research worlds. Taylor ended that particular programme with an explosion: *"….the last word on methodology….must go to the anonymous political insider who recently characterised the present Government's approach to research in the following manner:* ***it is not, he said, so much evidence-based policy-making as policy-based evidence-making****"*. Never was there a truer word, as the ME community knows to its considerable cost: it has been saying so for many years but has been systematically denigrated and ignored.

That quotation is momentous because it exactly encapsulates the reality: it seems that forces intent on "eradicating" ME (and even removing those few medical stalwarts who support ME patients) are at work that defy belief.

Physicians who genuinely try to help those with ME are themselves victimised, in some cases being reported to the General Medical Council (as, for example, was Dr Gordon Skinner over his treatment of thyroid problems in some patients with ME, a problem whose existence certain UK "experts" refuse to acknowledge, and Dr Sarah Myhill, who was stopped from successfully treating ME/CFS according to her clinical expertise and who was falsely accused of medical malpractice – a charge that was subsequently withdrawn).

This "policy-based evidence-making" has now reached such an extent that it has been likened to a cancerous metastatic spread (Stephen Ralph, 25th June 2005: http://health.groups.yahoo.com/group/MEActionUK/). There could hardly be a better analogy: metastatic spread takes hold by replicating itself until it eventually dominates and overwhelms, just as the unsubstantiated views about ME of the Wessely School psychiatrists have spread throughout the medical profession, the media (perhaps through the activities of the Science Media Centre, where Simon Wessely is on the Scientific Advisory Panel), Government, and even some of the patients' support organisations.

Mark Seddon, a member of Labour's National Executive, told the BBC of his concern about the influence of Lord Sainsbury: "*In any other country, I think a government minister donating such vast amounts of money and effectively buying a political party would be seen for what it is – a form of corruption of the political process*" (www.gmwatch.org).

For some, the choice of an unelected biotech investor to be Science Minister was emblematic of the UK's corporate science culture. Not only was Lord Sainsbury in charge of the MRC, but he is also known to be a keen supporter of the Science Media Centre .

The Linbury Trust has published two portfolios on "Chronic Fatigue" (into which they subsume ME/CFS). Both were published by the Royal Society of Medicine (1998 and 2000). The Wessely School is well-represented and contributors include Simon Wessely, Trudie Chalder, Anthony David, Helen Cope, Anthony Cleare, Peter White, Michael Sharpe, Alison Wearden, Louis Appleby and Philip Cowen.

These two portfolios make disquieting reading. Suffice it to say that Anthony David and Helen Cope dismiss the neuroimaging findings, describing them as " *'abnormalities' of debatable significance"*, and that Philip Cowen thinks that up to 30% of "CFS" patients meet the criteria for major depression; his contribution is entitled "Abnormalities of Mood".

For the avoidance of doubt, Professor Cowen (a psychopharmacologist from Oxford who has co-authored on "CFS" with Michael Sharpe) is a member of the newly-convened MRC "CFS/ME Expert Group" chaired by Professor Stephen Holgate, as is Dr Esther Crawley, Professor Anthony Pinching and Professor Peter White.

Perhaps this explains why at the RSM meeting on 11th July 2009 Professor Holgate indicated that the MRC favours the *status quo* and that he wondered if change in relation to ME/CFS would in fact happen.

The amount of what appears to be frank misrepresentation in the PACE Trial by those professionals involved with it seems to call into question the validity of the whole PACE Trial and indeed, the scientific integrity of the MRC itself.

Unblinding / blinding

Page 59 of the Trial Protocol states: *"all research and therapy staff…are unblinded to therapy allocation"*, meaning that the PACE Trial could suffer from "assessor bias" described by Lynch, Laws et al (Cognitive behavioural therapy for major psychiatric disorder: does it really work? A meta-analytical review of well-controlled trials. Psychological Medicine 2009:1: DOI:10.1017/S003329170900590X). Lynch et al focused particularly on methodologically rigorous trials that compared CBT with a "psychological placebo" and also investigated the impact of blinding, ie. whether or not the people who assessed the patients knew if they were receiving active treatment or not. The authors noted that not a single trial employing both blinding and placebo has found CBT to be effective in schizophrenia and surprisingly few well-controlled studies of CBT in depression: "'*The results of this review are important because in March NICE re-approved CBT for use in all people with schizophrenia. The Government is also investing millions of pounds to provide CBT for depression and anxiety in 250 dedicated therapy centres across England' said Professor Laws. 'Yet the evidence here is that the effectiveness of this form of therapy may be less than previously thought, to the point of being non-existent in schizophrenia' "* (ScienceDaily, 26th June 2009).

Even blinding at the PACE Clinical Trial Unit might not prevent inaccurate results because the data is known to be unreliable in any event.

One PACE Trial participant has openly said on the internet that it is very easy to lie to the Investigators to offset their coerciveness and their bullying tactics: in one particular case, the therapist insisted that the

participant exercised when it was simply not possible, so the participant reluctantly lied to the therapist in order to stop being put under such pressure.

There is no shortage of such information on internet messageboards, for example:

"I was pressurised by my family, GP and Dr X to go on (the PACE Trial) and it seriously set me back. I only managed 3 sessions, and was bedridden afterwards (on top of the above, I had an hour's journey each way in a cab). As I said, most of the excessively long sessions were spent filling in questionnaires which were psychological assessments….These were never discussed or used to further my treatment or recovery, ***so I amused myself by giving fictitious answers****"* (http://www.bbc.co.uk/ouch/messageboards/F3611783?thread=5747203).

Thus there is no guarantee that the data is accurate, so this cannot be in any way a scientific trial as there are no objective, scientific outcome measurements. To claim it as such is thus misleading.

Furthermore, self-report questionnaires upon which the data is to be analysed may not correlate with objective measures of activity (such as that provided by actometers which were used only at the start but not at the end of the trial).

It is surely curious that the reason given by the Wessely School for their rejection of patients' evidence (contained in the ME/CFS charities' questionnaires which found that CBT is ineffective and GET is actively harmful) is that self-report questionnaires are biased and therefore unreliable, yet the PACE Trial results are to be based on self-report questionnaires.

Apparent failure of the PIs to adhere to The Declaration of Helsinki

The Helsinki Declaration (World Medical Association Declaration of Helsinki, June 1964: Ethical Principles for Medical Research Involving Human Subjects) is a statement of ethical principles for medical research involving human subjects. It has gone through numerous amendments and it is intended to be read as a whole. The latest (6th) revision was October 2008, but the following quotations come from the 5th revision of October 2000.

There are numerous versions of the PACE Trial Protocol, and version 5 was the Final Protocol (1st February 2006). The full Protocol does not mention the Declaration of Helsinki, but the published (abridged) version of the Protocol (dated 2007) describes compliance as follows:

"***The trial will be conducted in compliance with the Declaration of Helsinki****, the trial protocol, MRC Good Clinical Practice (GCP) guidance, the Data Protection Act (1998), the Multi-centre Research Ethics Committee (MREC) and Local Research Ethics Committees (LREC) approvals and other regulatory requirements, as appropriate. The final trial publication will include all items recommended under CONSORT".*

In its Introduction (section A), the Declaration of Helsinki states:

A5: "*In medical research on human subjects,* ***considerations related to the well-being of the human subject should take precedence over the interests of science and society".***

A8: "*Some research populations are particularly vulnerable and need special protection…Special attention is also required for those… who may be subject to giving consent under duress…and for those for whom the research is combined with care".*

A9: "*No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration".*

Section B covers ***"Basic principles for all medical research".***

B11 states: "*Medical research involving human subjects must conform to generally accepted scientific principles (and)* ***be based on a thorough knowledge of the scientific literature".***

B13 states: "***The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations (and) other potential conflicts of interest"***.

B17 states: ***"Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed".***

B19 states: "***Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research".***

B 20 states: "***The subjects must be*** *volunteers and* ***informed participants*** *in the research project"*

B21 states: "***Every precaution should be taken to respect the privacy of the subject (and) the confidentiality of the patient's information".***

B22 states: ***"Each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher,*** *the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal"*

B23 states: "***When obtaining informed consent…the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress***".

It appears that the PACE Trial does not conform to the Declaration of Helsinki in full, for example:

- patients and participants have asserted that coercion was used (breaching A8, B20 and B22)
- participants' confidential data was not kept securely and was stolen (breaching B21)
- the Investigators ignored the scientific literature that differentiates ME/CFS from "chronic fatigue" (breaching B11)
- the Investigators already know (as does Wessely, who oversees the PACE Trial Clinical Unit) that "***These interventions are not the answer to CFS***" (Editorial: Simon Wessely; JAMA 19th September 2001:286:11) and that "***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) (breaching B19)
- the Investigators' conflicts of interest were initially denied (breaching B22)
- participants were not informed of the potential risks inherent in the trial, in particular they were not informed about the known adverse consequences of aerobic exercise for patients suffering from ME/CFS, for example, the effects of increased oxidative stress; the effects on cardiac output and function, or the effects of exercise on the (already disordered) immune system of ME/CFS patients (breaching A5, B20 and B22).

A cultural, not a medical, problem

As Hillary Johnson, author of "Osler's Web: Inside the Labyrinth of the Chronic Fatigue Syndrome Epidemic" (Crown Publishers, Inc. New York 1996) says in her article "Across the Pond, Part One, August 2009:

*"**It's hard to imagine a general patient population that has suffered more horribly than the English, given the remarkable sway of a handful of British psychiatrists, such as Simon Wessely, who dominate and even define the field there. This cabal continues to propose ever more preposterous explanations for the emergence of this disease in England, their influence leading directly to the incarceration of patients in psychiatric wards, the arrest of parents of patients, one might even claim the death of patients, and certainly all manner of abuse in the realm of treatments and therapy*** (http://www.oslersweb.com/blog.htm?post=623914).

It is almost as though the Wessely School diagnose "CFS/ME" by accusation and seem only too willing – if not eager -- to dispense with the rules of rigorous scientific analysis when it comes to their model of the biopsychosocial construct.

Common sense would suggest that it is better to admit to not understanding something than to construct implausible and untestable theories to hide ignorance.

The Wessely School's disregard of what is already known about ME/CFS seems to have had the effect of uncovering two undesirable characteristics in many clinicians who deal with ME/CFS patients: (i) an inability to admit ignorance and (ii) contempt for patients they perceive as somatisers. Far too many patients with ME/CFS can testify to the fact that doctors are willing to forget about medical science because of their strong antipathy to anyone with the label of "CFS/ME" and are quite happy to subject them to "punitive" regimes of CBT/GET, even though the Wessely School's model is not data-driven but merely opinion.

In many respects, the problem that patients with ME/CFS face is cultural, not scientific.

Despite the numerous and significant scientific advances internationally in understanding the nature of ME/CFS, the assiduous efforts of the Wessely School have ensured that UK clinicians' attitude towards patients with ME/CFS has undoubtedly worsened since 1987 when Simon Wessely came to prominence, and the immeasurable suffering of people with ME/CFS continues unabated.

Many people firmly believe that patients are subjected to what can only be described as medical abuse and neglect because of the way in which the Wessely School has portrayed ME/CFS as a behavioural disorder.

Patients with ME/CFS are still ridiculed and dismissed by their doctors and the DWP is increasingly targeting and harassing people with ME/CFS.

It is the case that on the very day that one of the people who sought information about the PACE Trial under the FOIA received that information, the applicant also received notification to attend a DWP Tribunal for re-assessment of benefits. It is also the case that when duly attending the DWP Tribunal, on the instruction of the Examining Medical Practitioner the applicant was refused entry to the Hearing until an intimate body search for weaponry had been carried out. Such intimidatory tactics perpetrated by the DWP upon an extremely sick and vulnerable ME sufferer are inexcusable.

Of overwhelming importance is the fact that, in rejecting the biomedical evidence that exists about ME/CFS, the Wessely School and the agencies of State to which they are advisors are simply wrong about ME/CFS. It is not a continuum of chronic fatigue, but a distinct nosological entity that, like multiple sclerosis, causes incapacitating physiological exhaustion.

To combine all states of "medically unexplained fatigue" into one non-existent functional somatic disorder and persistently to ignore the biomarkers that distinguish ME/CFS from psychiatric disorders seems not only perverse and thus unethical, but is deeply flawed and lacks scientific rigour, important issues which seem not to trouble Wessely School psychiatrists and their paymasters, nor the West Midlands MREC.

Many "Big Names" are involved with the PACE Trial

Many "big names" in the medical and scientific community are – or have been – involved with the PACE Trial. For the most part, these are people who have either stood back and/or have actively assisted, even though they have a responsibility to the public to expose and oppose what can only be described as a travesty of medical science.

For them not to have done so has put their reputations on the line because it is an appalling indictment of the state of medical research/funding in the UK and how this has become entangled in quick-fix politics and corporate control of the nation's health.

Some of those "big names" include:

Professor Colin Blakemore

Formerly Professorial Fellow at Magdalen College and Waynflete Professor of Physiology at the University of Oxford, between 2003 – 2007 Professor Blakemore served as Chief Executive of the MRC and is now Professor of Neuroscience at Oxford. He is a Fellow of the Royal Society and the Academy of Medical Sciences, amongst many other prestigious institutions, and has received numerous awards. Together with Simon Wessely, Blakemore works with and for the Science Media Centre and with its sibling organisation Sense about Science.

Soon after his appointment to the MRC, The Sunday Times published a leaked British Cabinet Office document that suggested Blakemore was deemed unsuitable for inclusion in the New Year's Honours List because of his research on animals, whereupon he threatened to resign. He withdrew his intention after expressions of support for him from the Minister for Science, Lord (David) Sainsbury. As of 2007, Blakemore was the only MRC Chief Executive unrecognised by the British honours system. In 2003, a House of Commons Select Committee criticised Blakemore for his *"heavy handed"* lobbying of other members of the National Institute for Medical Research taskforce.

An interview with him on BBC Radio 5 Live broadcast on 22nd February 2005 encapsulated the essence of the iatrogenic problem that for over two decades has compounded the suffering of those affected by ME/CFS in the UK. If Professor Blakemore's pronouncements had been about any other officially classified neurological disorder but the one in question, he would surely have been pilloried by the media and the public.

In the interview, Blakemore was asked *"**why, after several years of promises, the Medical Research Council has so far failed to fund any biological research into the physiological issues surrounding ME/Chronic Fatigue Syndrome that is recognised by the World Health Organisation as being a disease of neurological origin? Thus far the MRC has been seen to do not a lot more than perpetuate the status quo of funding psychological interventions (that) do not address neurological, cardiological, immunological and other abnormalities highlighted in international research that so far has been ignored in the United Kingdom".***

In response, Blakemore said: ***"I think to concentrate on this question of whether ME is thought to be a neurological or a psychological condition actually isn't going to get us far*** *--- I mean, compare the situation with depression: depression is a brain condition but depression can be treated both by psychological approaches and by drugs, so I don't think we should look down our noses at psychological treatments. We accept that this is a real disease (but) we don't understand its basis. We need high quality proposals –* ***I think everyone would agree that they***

wouldn't want taxpayers' money wasted on bad science however important the cause" (Co-Cure ACT: Transcript of Radio 5 Live 23rd February 2005).

In his justification of the MRC's position, Blakemore used the analogy of depression, but if he had used Parkinson's Disease or multiple sclerosis, the analogy does not work. Perhaps without realising it, Blakemore articulated that the MRC does not recognise ME as a "proper" neurological disorder.

Blakemore's assertion that there is no need to worry about whether or not the disorder is either psychological or neurological would seem not to be in accordance with the rigorous approach that is necessary for progress to be made in medical science. Did he really see no need to search vigorously for the cause of ME? If so, why does such an approach relate only to ME and not to all illnesses whose cause is as yet unknown, including cancer, multiple sclerosis and lupus? What is the purpose of the MRC if not to conduct research into illness that will provide understanding of (and result in treatment for) a disease?

Certainly no-one wants taxpayers' money wasted on bad science, yet that is exactly what many people believe is happening with the PACE Trial. 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".***

The ME Association has been adamant that the PACE and FINE trials 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".*

The ME Association additionally called for all further work on the FINE trial to be halted, saying the MEA *"is not convinced by the evidence so far put forward in support of this approach".*

Blakemore, however, was unmoved. By letter dated 11th May 2005, he wrote to an independent ME researcher about the PACE and FINE Trials: ***"I reiterate that the trials were peer reviewed and awarded funding on the basis of the excellence of the science".***

Section 2 of this Report has attempted to show why Blakemore's belief in the "*excellence of the science"* was misplaced.

Trial Investigators are required to look at a clearly-defined patient cohort but – against the WHO rules of taxonomy -- the PACE Trial Investigators intentionally amalgamated different disorders from the outset because, in defiance of the 193 member states of the World Health Assembly (of which the UK is one), the Wessely School insists that ME is a somatoform (behavioural) disorder so, as frequently noted above, **the**

PACE Trial includes those who do not have ME, yet claims to be studying those with ME. How does this accord with "*the excellence of the science*"?

As long ago as 1997, Professors Jason and Friedberg et al were scathing about physicians who interpreted the syndrome as being equivalent to a psychiatric disorder: *"We believe it is crucial for (ME)CFS research to move beyond fuzzy recapitulations of the neurasthenia concept"* (American Psychologist 1997:52:9:973-981), yet the West Midlands MREC approved -- and the MRC granted -- millions of pounds sterling for exactly such "*fuzzy recapitulations of neurasthenia".*

At the Royal Society of Medicine conference on 11th July 2009, MRC Professor of Clinical Immunopharmacology Stephen Holgate acknowledged that the history of research into ME/CFS had been appalling and that the historical link to neurasthenia was "*a major problem*", referring to that link as a virtual "*decaying circle*" and saying that there is a need for some "*truth and reconciliation*", yet the MRC seems to be intent on remaining in the dark ages.

As Demitrack made plain: "***To appropriately design and implement (successful interventions), it becomes critically important to specify the patient population most likely to benefit from the proposed intervention. 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***" (Pharmacogenomics: 2006:7(3):521-528). Under the guidance of Professor Blakemore, the MRC seems to have perpetuated the impediment to real progress towards effective therapeutics for ME/CFS patients.

<u>Professor Paul Dieppe</u>

Professor Dieppe is Chair of the MRC Data Monitoring and Ethics Committee. His committee (which included liaison psychiatrist Dr Charlotte Feinmann and epidemiologist Professor Astrid Fletcher) contributed to the design of the PACE study.

Professor Dieppe has a long and distinguished career record; he is Chair of Clinical Education Research in the Institute of Clinical Education at Peninsula Medical School (where Professor Anthony Pinching now works), prior to which he was Honorary Professor of Health Services Research at the University of Bristol where he served as Dean of Medicine from 1995-1997; he was an MRC Senior Scientist, then Professor in musculoskeletal science and Senior Research Fellow at St Peter's College, University of Oxford; he was an Honorary Consultant Rheumatologist at the Nuffield Orthopaedic Centre, Oxford.

<u>Dr Charlotte Feinmann</u>

Dr Feinmann is Reader in Liaison Psychiatry at University College London (UCL) Department of Mental Health Services; she is particularly interested in the role of psychiatric diagnosis and in the use of psychiatric screening questionnaires in liaison psychiatry and she has collaborated in a comparison of cognitive therapy and drug therapy with facial pain patients.

<u>Professor Astrid Fletcher</u>

Professor Fletcher is Director of the London School of Hygiene and Tropical Medicine's Centre for Ageing and Public Health. From the public health perspective, she is interested in estimating health needs for policy and planning.

Professor Janet Darbyshire, OBE

Professor Darbyshire is Chair of the PACE Trial Steering Committee, which includes Professor Jenny Butler (an occupational therapist), Professor Patrick Doherty (a physiotherapist) and Professor Tom Sensky (a liaison psychiatrist and CBT therapist). Previous members include Professor Clair Chilvers. Observers include Professor Mansel Aylward (see above and Appendix V).

Professor Darbyshire is an epidemiologist and science administrator who joined the MRC in 1974; she is the Head of the MRC Clinical Trials Unit and Joint Director of the UK Clinical Research Network (UKCRN) Co-ordinating Centre, which is one of the key components of the UK Clinical Research Collaboration (UKCRC), the latter being a partnership of organisations working to establish the UK as a world leader in clinical research by harnessing the power of the NHS.

Professor Jenny Butler

Professor Butler is a member of the College of Occupational Therapists (of which she was Head from 2004 – 2006) and a member of the British Psychological Society. Her first degree was in applied psychology at the University of Wales. She was made Honorary Fellow of the University of Cardiff in 2005 (where Professor Mansel Aylward now works). She was Chair of one of the three NHS research ethics committees in Oxford for over five years and was part of the inaugural committee for the Association of Research Ethics Committees (UK). She is on record in the Minutes of the joint meeting of the TSC and Data Monitoring and Ethics Committee on 27th September 2004 as stating that she was *"very impressed"* with the CBT Therapists' Manual, which included recommendations advised by Professor Tom Sensky (see below for his views on ME/CFS).

Professor Patrick Doherty

Professor Doherty is a physiotherapist who now holds the Chair of Rehabilitation at York St John University. He is Clinical Specialist in Cardiac Rehabilitation at York Hospitals NHS Foundation Trust and is a member of the Department of Health's dual tariff group for cardiac surgery and rehabilitation. He is also President of the British Association for Cardiac Rehabilitation and is National Clinical Lead for Cardiac Rehabilitation (NHS Heart Improvement).

(Professor Doherty's expertise in cardiac issues thus ought to have placed him in an advantageous position in relation to the cardiac problems in ME/CFS).

Professor Tom Sensky

Professor Sensky from the Division of Neurosciences and Mental Health, Imperial College, London is, like Simon Wessely, a liaison psychiatrist and he practices cognitive behavioural therapy.

At the launch of The Psychological Medicine Network (established to *"facilitate knowledge and information sharing among staff providing psychiatric and psychological care for medical patients in London"*, whose aim is *"to identify and unify those working in psychological medicine in London in order to create better networking opportunities between individuals and services"* and to *"disseminate examples of good practice")* on 10th December 2004 at Regent's Park College, Sensky's presentation was entitled "*Somatisation and Primary Care"*, in which he made some disturbing statements (backed by his PowerPoint slides, some of which have now been removed from the internet) about patients with medically unexplained symptoms (MUS) in which he includes CFS patients.

In addition to numerous cartoons that denigrate sick people (one of which shows a woman sobbing in front of a doctor, with the caption "*Madam, this is a consultation, not an audition")*, Sensky's slides state, for example, that:

- *"People who present with somatisation disorders are often difficult to manage (and) may arose* (sic) *strong feelings in clinicians"*

- patients with a *"rating as 'difficult'* (are) *strongly associated with functional disorders"*

- *"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; that IBS patients do not have a low threshold for symptoms but that CFS patients do have a low threshold for symptoms; that IBS patients do not lack stoicism but that CFS patients do lack stoicism, and that IBS patients do not transgress the obligations of the sick role but CFS patients do transgress it.**

Sensky maintains that GPs make "*inappropriate referrals"* for patients with medically unexplained symptoms (MUS) 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: *"medical tests are logically ambiguous*"; 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 ME/CFS).

Why is someone holding such views about ME/CFS as Professor Sensky a member of the PACE Trial Steering Committee? Who approved his membership of the TSC?

It seems that he shares many of the same views about ME/CFS as Professor Simon Wessely so, as someone who seems to share Professor Wessely's views about ME/CFS, perhaps it is unsurprising that he is involved with the Wessely School's PACE Trial.

Perhaps it is also unsurprising that the authors of the PACE Trial Manuals repeatedly paint a picture of widespread institutionalised prejudice and contempt for ME/CFS patients from other professionals. Who, apart from Professor White, approved them?

<u>Professor Clair Chilvers</u>

Professor Chilvers has had an immensely distinguished career. A former pupil of Cheltenham Ladies' College, in March 2009 she was aged 63. She went to Nottingham in 1990 as Professor of Epidemiology, and from 1996 she was Dean of the Graduate School. She was appointed Regional Director of Research and Development (R&D) in the Department of Health at NHS Executive Trent in October 1999. She has been Head of R&D in the Midlands and East of England Directorate of Health and Social Care. She was Chair of Nottinghamshire Healthcare NHS Trust, which is one of the largest providers of mental health services in England. She has been a member of the Department of Health Committee on Carcinogenicity of Food, Consumer Products and the Environment from 1993 to 2000 and a member of the Royal Commission on Environmental Pollution from 1994 to 1998. Her research work at the Institute of Cancer Research in London involved studies on both breast and testicular cancer. She also has a degree in statistics and a

Masters in medical statistics, which led to being part of a team at the London School of Hygiene and Tropical Medicine that applied statistical expertise to research.

Together with Professor Colin Blakemore, she is a former member of the Mobile Telecommunications and Health Research Programme.

She has now moved into the field of mental health; she was Director of the National Forensic Mental Health Research and Development Programme for the Department of Health and is Chair and Trustee of the charity Mental Health Research UK, a charity which she helped to set up.

She is a Trustee of the Lloyds TSB Foundation and is a Deputy Lieutenant of Nottinghamshire.

There is, however, one milestone that seems not to feature prominently in her prestigious CV, and that is her 1990 Chilvers Report (Survival of patients with breast cancer attending the Bristol Cancer Help Centre. Chilvers C, McElwain T et al. Lancet 1990:336:8715:606-610). One of her co-authors, Professor Tim McElwain from the Institute of Cancer Research and the Royal Marsden Hospital, was a founder member of HealthWatch (then called the Campaign Against Health Fraud), a UK organisation -- now a charity -- that was known for its zealous antagonism towards alternative and complementary medicine. HealthWatch literature proclaims that its aims are *"to oppose…unnecessary treatment for non-existent diseases"* and the same document lists Simon Wessely as a *"leading member of the campaign"* who, as noted above, is on record as regarding ME as a *"non-existent disease"*. HealthWatch is a campaigning organisation that has accepted funding from the pharmaceutical and health insurance industries (for more details, see http://www.meactionuk.org.uk/CONCEPTS_OF_ACCOUNTABILITY.htm).

The Chilvers Report concluded that those women with breast cancer who sought help from the Bristol Cancer Help Centre (BCHC) were more likely to die than those who did not. This finding very nearly obliterated the BCHC and the staff who supported it but, beleaguered though they were, the staff fought back with tenacity.

The result was that the Chilvers Report was found to be seriously flawed and was retracted by the authors (Lancet: 1990:336:8724:1185-1188).

There are, of course, other "big names" involved with the PACE Trial.

The question to be asked is simple: how can such undoubtedly distinguished academics and clinicians not have been aware of the controversy engendered by the Wessely School about ME/CFS?

How could they not be aware of the evidence set out in Section 2 above that was published at the time?

How could they not be aware of their ethical responsibilities?

Are all these people guilty of a dereliction of duty in that they seem not to have put the best interest of patients with ME/CFS above the interests of the PACE Trial Investigators?

Were they simply misled by Professor White? Why did they not check for themselves the authenticity of his beliefs against the available science?

Had they done so, they might have seen that the Wessely School, for example:

- have significant financial conflicts of interest
- have used entry criteria for the PACE Trial that do not define the patient population they purport to be studying

- have succeeded in making clinicians fearful in case they may be thought (or worse, to be shown) to have been taken in by "malingering" ME/CFS patients – as the Medical Advisor to the ME Association recently said: "*a significant number of my good medical colleagues are…reluctant to get involved with ME/CFS*" (http://health.groups.yahoo.com/group/MEActionUK/, 6th November 2009), which has been translated by the listowner as: "*Keep quiet about psychiatry. Keep quiet on asking for bio-medical research. Play the game our way, otherwise don't speak. Right, guys?*". It is undoubtedly true that most ME/CFS patients know more about their disease than most doctors, a situation which some doctors might find humiliating and therefore do not allow it to present itself by referring the hapless patient into psychiatric care
- have portrayed people with ME/CFS as feckless, suggestible malingerers who are afraid to exercise their deconditioned bodies (a concept that fails to consider the countless academics, scientists, clinicians and lawyers who have been forced to lose their cherished careers)
- have mis-portrayed ME/CFS patients to PACE Trial therapists, which lowers the respect that therapists should have for their patients
- have instructed therapists to mislead participants by pretending that they believe participants are suffering from a physical disease when therapists have been taught otherwise
- have taken away participants' autonomy
- have implied criticism of other medical professionals who do not subscribe to the Wessely School's beliefs
- have mis-portrayed and trivialised ME/CFS as a dysfunctional belief
- have based their model of "CFS/ME" on empty and illogical arguments that have long since been discredited in the international literature
- have portrayed as established facts what they themselves acknowledge to be unproven assumptions
- have purloined ideas from other fields that have no relevance whatever to ME/CFS (see Appendix VI).

In other words, the PACE Trial appears ill-conceived pseudo-science and a deplorable waste of UK taxpayers' money as well as doing nothing constructive to alleviate the suffering of people with a serious and life-destroying disease.

No matter that:

- the WHO has classified ME as a neurological disorder for forty years
- there are over 5,000 published papers demonstrating serious organic pathology in ME/CFS
- the Royal Society of Medicine accepted ME as a nosological entity in 1978
- the UK Department of Health accepted ME as a physical (organic) disease in 1987
- the British Medical Association issued a statement saying that ME was "*a newly recognised **disease** and that we are sympathetic to sufferers*" in 1988
- people in the UK with ME have been **permanently** excluded from donating blood since at least 1989 (Guidelines for the Blood Transfusion Service in the UK, 1989: 5.4; 5.42; 5.43; 5.44; 5.410)
- the UK Disability Living Allowance Board accepted ME as a physical disorder in 1992
- the UK Health Minister went on record stating "**ME is established as a medical condition**" in 1992
- the UK Chief Medical Officer went in record in 2002 stating that ME should be recognised alongside disorders such as multiple sclerosis and motor neurone disease
- ME has been classified as a neurological disorder in the UK Read Codes (F286) used by all GPs since 2003
- the UK Health Minister confirmed that the Department of Health accepted the WHO classification of ME (ie. as neurological) in 2004
- ME has been included in the UK National Service Framework for long-term neurological conditions since its inception in 2005
- ME is accepted to be (as well as being classified by the WHO as) a neurological condition by the UK Government as recorded in Hansard in 2008,

yet ME does not exist -- Professor Wessely and his acolytes say so, and the MRC apparently accepts the Wessely School's beliefs.

Commenting on the tragic case of Pamela Weston (an ME sufferer who committed suicide at the Dignitas clinic in Switzerland), on 27th September 2009 Dr Matthew Harris from Exeter wrote in The Times online:

"*The assertion 'many doctors believe ME has a psychological rather than a physical cause' contradicts the Royal College of General Practitioners, which reclassified ME as a physical illness in August 2008.* ***The statement may be re-phrased to say a minority of psychiatrists think ME is psychological.*** *In fact, many doctors are hoping that the NICE guidelines will be amended to reflect the current understanding of ME as physical in origin and physiological in its development, so as to provide a more practical model for general practice".*

According to Professor Martin Pall, the PACE Trial is predicated on three obvious failures: (i) the psychogenic advocates fail to explain the vast amount of genuine pathophysiological changes found in sufferers of ME/CFS; (ii) the "biopsychosocial" construct is built on ignorance and its whole basis has no foundation and (iii) the Wessely School's claims that ME/CFS is a functional somatic syndrome are specious because there are biomedical explanations for the protean symptoms of ME/CFS.

It should not be forgotten that one of the PACE Trial's Principal Investigators, Professor Michael Sharpe, is on record thus: "*Purchasers and Health Care providers with hard pressed budgets are understandably reluctant to spend money on patients for whom there is controversy about the 'reality' of their condition (and who) are in this sense undeserving of treatment…Those who cannot be fitted into a scheme of objective bodily illness yet refuse to be placed into and accept the stigma of mental illness remain the undeserving sick of our society and our health service*" (ME: What do we know: real illness or all in the mind? Lecture given by Michael Sharpe in October 1999, hosted by the University of Strathclyde).

No matter what the latest UK Government policy happens to be, given the body of biomedical evidence that exists about ME/CFS, for the MRC to fund out of taxpayers' money trials that appear to have no scientific integrity or value seems indefensible.

<u>UK/US Interactions</u>

In the US ME/CFS was designated by the Centres for Disease Control as "**A serious legitimate diagnosis CDC Priority 1 Disease of Public Health importance"**, not as a behavioural disorder as in the UK. **However, it seems that it is no longer categorised thus, and that the Wessely School has set out to change that previous situation in the US in order to bring it in line with the situation in the UK, aiming at an "international consensus" about how "CFS/ME" should be managed.**

The Minutes of the Health & Human Services CFS Advisory Committee meeting on 27th and 28th May 2009 held in Washington DC record that Dr William Reeves of the CDC said that the CDC wanted to get together an international workshop on "CFS" by winter 2009: "***We want to include countries such as the UK that have CFS care completely integrated into their healthcare system….The collaboration with Peter White is largely because Peter White came to us when the National Health Service in the UK was trying to design its programme and formulate recommendations about what the health service in the UK should do…and we collaborate with Dr White on the PACE Trial. An international meeting provides the chance to learn from another government that has embraced this illness".***

The Chair of the CFS Advisory Committee, Dr Oleske, responded: ***"I have to say that I think there are times when the domestic agenda suffers at the behest of an international agenda"*** and a member of the CFS Advisory Committee (Ms Artman) said that when she had contacted those who participated in the CDC stakeholder meeting, ***"Just about everyone came back with comments about either Simon Wessely or Peter***

White treating this as a purely psychiatric disorder and not as a multi-system complex disorder. There's a perception that in working with the UK, (the US is) adopting that this is a purely psychiatric disorder*".*

Inexplicably, Dr Reeves went on to say: "*Peter White, the psychiatrist we work with, does not look upon CFS as a psychiatric illness – he is an expert on autonomic nervous system function and he's highly instrumental in all of the hurdles – both with patients, with the government and with physicians – in trying to put together a national programme".* As Tom Kindlon pointed out, most people would question why, if an expert in the autonomic nervous system were sought, a major body like the CDC would bring in Peter White (Co-Cure ACT: 1st October 2009), since there is no evidence that he is an expert on dysautonomia. Indeed, White's own words confirm this: the BBC programme "You and Yours" ran a series of interviews on ME/CFS in November 2007, and when asked by the interviewer about the Canadian Guidelines, Professor White said he did not like them: "*The problem is, and the reason why I don't use them, is they're very complicated to use and would require me actually to do tests on my patients that I don't think I ethically should be doing on my patients".* The interviewer then addressed Professor White: "*You mentioned tests that you don't think it's right for you to do, such as…?"*, to which Peter White replied: "*Such as the tilt table test. I would have to exclude a condition called POTS, where the blood pressure falls on standing up. I don't think that's justified".* The interviewer then asked Professor White: "*So you think they're unethical because they're too demanding?"*, to which Professor White responded: "*Yes"*. If Professor White were an *"expert on autonomic nervous function"*, then tilt table testing would be a routine test that he carried out.

Dr Reeves also said – categorically – that Peter White does not look upon "CFS" as a psychiatric illness. Again, this does not accord with Peter White's track record, which is that he regards it as a somatoform disorder.

Referring to Dr Reeves' "Introduction Before Public Stakeholders Meeting" in Atlanta, 27th April 2009 and his desire to have an international consensus on CFS, Dr Mary Schweitzer commented (Co-Cure 1st May 2009): "*I particularly noted (his) reference to the UK and the NICE Guidelines. I believe he said 'Dr Peter White is a representative of, I think, the only country and Ministry of Health in the world that has developed a comprehensive programme for diagnosing, evaluating and treating CFS'.*

" I have to pose a question that seems to me to be an ambiguity that continues to go unchecked within the research and the approach of the UK and the US.

"*The CDC asserts on its website that CFS is not ME.*

"Benign Myalgic Encephalomyelitis was identified and diagnosed in the UK and it is the entity that research there refers to now as CFS. CFS/ME is the compromise name. People with ME are lumped in with CFS, if they are studied at all.

"If the UK is including ME with CFS participants and the CDC knows this, and those NICE Guidelines cover both, how can the CDC refer to these Guidelines as representative of CFS?

"If ME exists as a discrete neurological entity with its own criteria (which the CDC says it does), then why doesn't the CDC have a research programme for it? It exists and they acknowledge it exists.

"If ME is being investigated <u>with CFS</u>, then why does the CDC allow this to continue while at the same time acknowledging ME is not CFS?

"Surely that (is) a clear case of muddying the waters and therefore making research unrepresentative of either ME or CFS?".

It does seem to be the case that the Wessely School has succeeded in muddying the US waters as well as the UK waters. The Minutes of the US CFS Advisory Committee meeting held on 27th –28th May 2009 in Washington DC record that:

- Professor Nancy Klimas said: *"The incidence of CFS is very similar to that of breast cancer"*
- Dr Bill Reeves from the CDC said: "*There is undoubtedly more than one sub-type of CFS…evaluation and management must take into account the multiple sub-types of CFS"*
- Dr Reeves said: *"CFS is a complex illness (and) CFS research may help us with other complex, ill-defined illnesses such as FM, post-infectious illness, interstitial cystitis, and multiple chemical sensitivities"*
- Dr Reeves said: "*We now know that the occurrence of metabolic syndrome is significantly elevated in people with CFS"*
- Dr Reeves said: "*(CFS) is not a trivial illness or a trivial burden on society or the patients"*
- Dr Reeves said that the CDC's Goal 1 was to "*Improve our focus on measures of the neuroendocrine, metabolic, immune and infectious characteristics of CFS to identify targets for the various subsets of the illness"*; that Goal 2 was to *"Improve clinical management by providing evidence-based educational materials addressing evaluation and clinical management"* and to "*get current evidence-based information on diagnosis and treatment out to those who need it"*; that Goal 3 was to "*Improve diagnosis and management through research"* and that Goal 4 was to *"Move CFS into the mainstream of public health concern"*
- Dr Reeves said: *"We are in the process of planning a cognitive behavioural therapy (CBT) and graded exercise (GET) trial…We're going to do that in collaboration with…the UK group. Obviously CBT/GET is not the cure for everybody. Nobody knows for how many it is. It probably applies to a subset"*
- Professor Klimas said: ***"CFS is the most broken illness there is that I know of in terms of being misunderstood and misrepresented"***
- Professor Klimas said: ***"(Dr Reeves), when you were talking about doing a workshop on management, diagnosis, and evidence-based research, they were in the wrong order. You're doing the evidence-based thing last, which doesn't inform the other two processes".***

The MRC PACE Trial is doing exactly what Professor Klimas said was in the wrong order: it is intent on showing that one particular form of "management" is efficacious without having first done the biomedical research that would aid diagnosis. This approach defies logic.

It appears that the Wessely School influence increasingly pervades the US as well as the UK, but it is noted that with effect from 14th February 2010, Dr Reeves will no longer lead the CDC's CFS research programme (Co-Cure NOT: 29th January 2010), which may affect Peter White's present working relationship with him.

In her testimony to the US Health & Human Services CFS Advisory Committee on 27th-28th May 2009, Jean Harrison, a long-term ME/CFS patient and advocate, said:

"You will undoubtedly have heard that the definition of the illness which has come to be known as chronic fatigue syndrome is too broad. It is. The International Consensus Definition of 1994 was a travesty. We were told that broadening the 1988 definition would result in better research, a greater likelihood that a cause of the illness would be discovered. Fifteen years later and we are far from seeing any indication that that assumption is correct. Those who got together for the consensus definition are still far apart. Their opinions are as polarized as they were when they created that research definition.

"Which brings us to a question: why try to have a consensus definition at all? Science is not about consensus; it's about finding truth. Science is not democratic. If opinions vary as dramatically as they do re: CFS there is no point in trying to find a middle ground. While one group continues to do fine research into biological processes which cause our symptoms, the other steadfastly refuses to recognize that research. Are they aware of it? Do they read it? Do they even attempt to disprove it? No. The latter group simply insists that CBT & graded exercise effectively treat CFS, but ask them to define CFS & you will find that they consider it a somatization disorder, F48 in the ICD-10. No consensus; flat out disagreement as to the nature of the disease.

" Attempting to come to a consensus between two opposing groups was a mistake and is at best questionable scientific method.

"It's time to adopt the Canadian Criteria, which at least are written by clinicians who have long dealt with those suffering from the malady once known as myalgic encephalomyelitis. The further one gets from actual case studies, the further one gets from finding a way to ease suffering. It is unacceptable for one group of theoreticians to ignore replicable scientific studies and be considered the equal of those who approach the illness scientifically. ***You are playing with a lot of lives and a great deal of suffering****".*

As US ME/CFS sufferer John Herd noted: *"The English healthcare system has openly committed itself to a proposed behavioural model for the illness and behavioural treatment approaches"* (Co-Cure ACT, 19th August 2009).

This is a matter of international concern and comment: Dr Alan Gurwitt, a US psychiatrist who does not subscribe to the Wessely School's behavioural model of ME/CFS, expresses his dismay and frustration:

"*Nationally and from around the world, the stories are much the same. People with CFS/ME, adults or children, suffering from multiple symptoms, with varying degrees of severity, are dismissed and improperly diagnosed or treated. They are either told that it's all in their heads or yes, it might be CFS/ME but there is nothing much that can be done for it. And yet the patterns of CFS/ME, the diagnostic steps necessary, and the treatment possibilities are clear enough to those health professionals who are knowledgeable about them and who are aware that there is much that can be done to help. Why still are so many other physicians relatively ignorant about or dismissive of CFS/ME? Is there not sufficient information available? There is now a wealth of good information available from research and clinical experience. Is skepticism as to the realities of CFS/ME and FM still so prevalent that there is little or no motivation to learn about these illnesses? Well, sadly, yes. Are the relative ignorance and skepticism important? They sure are, as testified to by patients around this state and elsewhere. Are the skepticism and relative ignorance even harmful, causing unnecessary suffering? Most certainly yes. The lack of correct diagnosis, treatment steps not taken, disdainful and dismissive attitudes do hurt people. Are the skepticism and ignorance simply the result of individual physician decisions? Not at all. The CDC and NIH in the USA, the NHS in the UK, medical societies and medical schools, and prestigious journals, no matter what is said, if anything, SHOUT, by means of their silence or lack of effective action, their disinterest and disbelief. It is the brave physician who dares to be curious, to look for information, to climb over this wall of disdain and ignorance. These skeptics predominate in government, medical school and journal hierarchies so they have, in effect, blocked and can continue to block the research and clinical teaching necessary to change the picture. In my experience there are at least two root causes for the prevailing ignorance among physicians and other health professionals. One is simply lack of familiarity with the now ample scientific understanding of CFS/ME and its diagnosis and treatment. The second is a kind of "old boy bias", opinions formed many years ago, passed on by a form of group-think as the proper and prevailing views, untouched, unexamined, unchanged, and driven by an unwillingness to learn about the new research. Perhaps this situation will change once irrefutable biomarkers are real, but in the interim much harm is being done, much relief not provided. Every week I hear more of the stories of misdiagnosis and mistreatment from within our state and beyond, some of the stories more egregious than others. When is enough ignorance enough? Do we just sit back and keep our fingers crossed or try harder to find ways to make up-to-date information available? Or when the stories of ignorance and harm being done pile up in relation to a particular medical school or institution, or government agency or physician, should we take constructive action? Nor will any of this change until attitudes, not just evidence, change. Yes, we need biomarkers, but there is enough evidence now to spur new learning. When the evidence is there, but the will to study it is not, and then harm is done out of this ignorance, does that become an ethical issue, rather than a scientific one? When is enough (ignorance) enough?"* (Co-Cure ACT: 19th August 2009).

As mentioned above, US expert Professor Leonard Jason et al point out that *"****measurement that fails to capture the unique characteristics of these illnesses might inaccurately conclude that only distress and unwellness characterise these illnesses, thus inappropriately supporting a unitary hypothetical construct called functional somatic syndromes****"* (JCFS 2007:14(4):85-103), but neither the Wessely School nor UNUMProvident seems even to consider the need to capture the unique characteristics of ME/CFS.

Two years after publication of that article, Jason, Najar, Porter and Reh investigated the Reeves et al 2005 CDC empirical case definition of "CFS" (http://www.biomedcentral.com/content/pdf/1741-7015-3-19.pdf) and found that it had "*broadened the criteria such that some individuals with a purely psychiatric illness will be inappropriately diagnosed as having CFS"* and that "*Inappropriate inclusion of pure psychiatric disorders into the CFS samples may further contribute to the diagnostic skepticism and stigma that individuals with this illness encounter. Several researchers continue to believe that CFS should be considered a functional somatic syndrome"*. Jason et al repeat their warning given in 2007: "*assessment and criteria that fail to capture the unique characteristics of these illnesses might inaccurately conclude that only distress and unwellness characterise CFS, thus inappropriately supporting a unitary hypothetical construct called 'functional somatic syndrome'. Such blurring of diagnostic categories will make it even more difficult to identify biological markers for this illness, and if they are not identified, many scientists will be persuaded that this illness is psychogenic"*. Jason et al note that, using the Reeves et al criteria, 100% of the MDD (major depressive disorder) group met the Reeves et al CFS criteria, indicating that the Reeves et al criteria do not distinguish between people with CFS and MDD.

The prevalence rate for the Reeves et al 2005 empiric criteria is 9.69 times the CDC 1994 Fukuda criteria; put another way, only 10.31% of those who satisfy the Reeves et al empiric criteria would satisfy the CDC 1994 Fukuda criteria, which themselves do not identify people with Ramsay-defined ME: ie. a person could satisfy the CDC 1994 Fukuda criteria and still not have ME (Tom Kindlon. Co-Cure ACT 3rd November 2009, who also pointed out that in one of the Reeves et al studies, medical exclusions included an abnormal Romberg test, which is curious, given that it is used to support a diagnosis of Ramsay-defined ME).

Jason et al also note that the Reeves et al case definition *"does not distinguish critical symptoms for CFS such as postexertional malaise"* and that as a result, the estimated rate of "CFS" has increased about ten times higher than previous estimates of both the CDC and other researchers, which brings it within the range of several mood disorders. Jason et al comment: "*It is possible that using this broadened CFS empirical case definition, some patients with a primary affective disorder could be misdiagnosed as having CFS.* ***Some CFS investigators would not see this as a problem because they believe that CFS is mainly a psychiatric disorder and that distinctions between the two phenomena are superficial and merely a matter of nomenclature***" (Evaluating the Centres for Disease Control's Empirical Chronic Fatigue Syndrome Case Definition. Leonard A Jason et al. Journal of Disability Policy Studies 2009:20:2:93-100).

Abuse of Process?

It cannot be reiterated enough that many people – including patients with ME/CFS, their families, academics, medical scientists, informed clinicians – are deeply dismayed by the apparent abuse of the scientific process that seems to have been perpetrated by the MRC, the Principal Investigators and indeed by all those involved with the PACE Trial.

In March 2003 the House of Commons Select Committee on Science and Technology produced its Report "The Work of The Medical Research Council" (HC 132) in which MPs issued a damning judgment on the MRC, lambasting it for wasting funds and for introducing misguided strategies for its research. The Select Committee had received seven representations about the MRC's refusal to heed the biomedical evidence about ME/CFS. MPs found evidence of poor planning and of focusing on "politically-driven" projects that have diverted money away from top-quality proposals. The unprecedented attack was the result of a detailed probe into the workings of the MRC. In particular, MPs questioned why the MRC was content to support policies and projects that are likely to perpetuate such criticism.

The most obvious questions arising are (i) why should psychiatrists and a behavioural therapist be carrying out clinical trials on people with a complex neuro-immune disease and (ii) what are their motives for doing so? The evidence points to the possibility, indeed the likelihood, that patients' needs are of secondary, not primary concern, because the objective of the Trial seems to be to reduce the number of people with

"CFS/ME" on State benefits and as a corollary, to reduce payments by insurance companies to those with ME/CFS.

Wessely School psychiatrists are not neurologists, immunologists, neuroendocrine experts, vascular medicine experts, or nuclear medicine experts, all of which are outside their area of expertise, so how do they justify their involvement with and catchment of patients whose disease processes affect multiple organs and systems, given that they are not qualified to investigate or explain complex diseases for which there is as yet no definitive diagnostic test? Indeed, Wessely is on public record boasting that he does not understand immunology: at his Gresham College lecture on 25th January 2006 ("Something old, something new, something borrowed, something blue: the true story of Gulf War Syndrome"), he stated about the immunology of Gulf War Syndrome: *"This is going a bit beyond me here"* (http://gresham.ac.uk/event.asp?PageId=0&EventId=448). Indeed, two years earlier, on 10th August 2004 in his evidence to the Lord Lloyd of Berwick Independent Inquiry into Gulf War Illnesses, when discussing immunology and the shift from Th1 to Th2 (as has been shown to occur in ME/CFS also), Wessely said: *"Now, please do not ask me what that means because I do not really know. A man has got to know his limitations and my limitations are immunology"* (www.lloyd-gwii.com/admin/ManagedFiles/2/GWI1008%2000.doc).

Why are behavioural interventions even on the agenda for a disease described by Professor Nancy Klimas from Miami at the MRC/Action for ME Workshop in November 2006 as having an increase in class II antigens HLA DR4, DR5, DQ3 and an immune response that has persistently shifted to the Th2 system so the Th1 system does not function properly? (HLA antigens are responsible for the immune system being activated to detect and eradicate foreign bodies; Th2 cytokines activate B-cells, which in turn results in the production of auto-antibodies which can trigger autoimmune disease, as well as multiple allergic / hypersensitivity reactions).

Put another way, how can behavioural interventions such as re-educating the mind to believe that ME/CFS does not exist as an organic disorder possibly be effective in restoring the immune system dysregulation (including the chronic immune activation) that is characteristically seen in ME/CFS? Such mind-changing "interventions" are not the same as providing support and help in managing a life-shattering disease.

Self-proclaimed "experts" in disorders in which they are not medically qualified cannot always be relied upon and such experts need to be rigorously questioned as to the source of their "evidence", as was made clear on 15th July 2005 by the Chairman of the General Medical Council (GMC) Panel, Mary Clark-Glass, who was excoriating about one self-proclaimed expert (Professor Sir Roy Meadow):

"Your misguided belief in the truth of your arguments maintained throughout the period in question and indeed throughout this inquiry is both disturbing and serious. You should not have strayed into areas that were not within your remit of expertise" (http://www.meactionuk.org.uk/Another_Meadow.htm).

Straying into areas that are not within their area of expertise is widely believed to have become the hall-mark of Wessely School psychiatrists (for example, ME/CFS; fibromyalgia; irritable bowel syndrome; interstitial cystitis; Gulf War Syndrome; multiple chemical sensitivity; repetitive strain injury).

Attention has been drawn in Sections 1 and 2 above to the involvement of psychiatrists in the totalitarian regime in Nazi Germany in which the individual was subjugated to the over-arching "needs" of the State and in which the ethos and ethics of medicine were manipulated to achieve that goal.

It was not, of course, only the Nazi regime which distorted the care of the sick and vulnerable: as Robertson and Walter point out: *"medical ethics, and in particular, psychiatry, has lost sight of the Hippocratic tradition, a process arguably brought about by the invasion of third-party payers as part of the doctor-patient relationship…Historical aspects of psychiatric ethics have been well-documented….including the abuses of psychiatry in the Nazi era, the Soviet era (and) modern-day China…**Radden holds that the special virtues required of the psychiatrist are compassion, humility, fidelity, trustworthyness, respect for confidentiality, veracity,***

prudence, warmth, sensitivity and perseverance*….the Hippocratic tradition in medicine has been swept aside by the combined effects of changes in society, in particular, the commercialisation of the health system"* (Overview of psychiatric ethics I: professional ethics and psychiatry. Australasian Psychiatry 2007:15:3:201-206).

Has this totalitarianism invaded medicine, especially psychiatry, in the UK and have the virtues required of psychiatrists been abandoned in their efforts to comply with the demands of their paymasters?

Is it the case, as demonstrated in a TV documentary, that multi-national corporations and not governments now control the world? Are powerful and influential psychiatrists who work within the Mental Health Movement linked to the multi-national corporations that now dominate and control medical and research institutions and whose life-blood is profit? (*Politics isn't working: the End of Politics. Cambridge academic Noreena Hertz presented evidence that multi-national corporations are taking the place of elected governments. ITV Channel 4, 13th May 2001).*

To the detriment of the sick, the deciding factor governing policies on medical research and on the management and treatment of patients is increasingly determined not by medical need but by economic considerations. Patients with ME/CFS are casualties of this corporate control.

Given that biomedical research, including gene research, has demonstrated that the psychiatrists who hold such sway at the MRC are comprehensively wrong about ME/CFS, nowhere could such criticism be more apposite than in relation to the PACE Trial, yet the imperium granted to these psychiatrists is virtually insurmountable.

On 28th October 2006, Consultant Dermatologist Nick Hardwick from Mid-Staffordshire General Hospital summed things up accurately: "*Over the past few decades the practice of Medicine has moved from a basis of personal experience and understanding of the disease process and its treatment towards the application of authorised protocols and guidelines. (The) article raises concern about the situation in which an inadequate evidence base has become canonised into established guidelines, Government policy and incentivised practice. It takes a bold man indeed to challenge this set of Emperor's clothes. Perhaps we need a forum to build up a sufficient groundswell of opinion to challenge the court tailors".* (Vested interests will always trump science. BMJ 2006:333:912-915).

It is salutary to recall the words of the Presiding Officer (Speaker) of the Scottish Parliament delivered at the ME Research UK international research conference on 25th May 2007 in Edinburgh; Mr Fergusson MSP said he had been contacted by a constituent asking for help: "*She's had ME for some time and been refused Disability Living Allowance and the State support that comes along with that on the grounds that whilst she has been recognised as having ME, she has not sought or been given psychiatric treatment****. Now that to my mind absolutely sums up the principal concerns of the Scottish Cross Party Group on ME, which is that the cold grip of psychiatry is still far too deeply rooted in the world of ME****".* (http://www.meactionuk.org.uk/Defiance_of_Science.htm).

Many doctors and ME/CFS patients alike hold the view that the Wessely School has been responsible for over two decades of the most blatant medical abuse of ME/CFS patients. One severely affected person wrote about the involvement of Wessely School members in the MRC PACE trial: ***"I think it profoundly disgraceful that any individual who has caused so much suffering to so many members of the public, including those affected by ME, is involved in this trial in any capacity"*** (letter to AfME, August 2007).

This particular "school" of psychiatry has, in the eyes of the ME/CFS community, caused untold damage, not only to patients but to the discipline of psychiatry, because they believe that the Wessely School perpetuates psychiatry's regrettable record of claiming unsustainable hypotheses as fact, to the harm of its victims, unknown numbers of whom have died.

As Douglas Fraser, a professional violinist badly affected by ME/CFS since 1994, has written: "*When (people with ME) are subjected to (this) type of professional abuse, one realises just how out of control and irresponsible*

segments of the medical establishment have become. When science and rationality are so easily eschewed, you know what kind of society we are now living in".

The consequences of opposing Wessely School ideology can be dire. When in January 2006 an organised peaceful protest was mounted outside a public lecture on Gulf War Syndrome to be given by Professor Simon Wessely at Gresham College, London, some chilling incidents occurred. One day before the event, strange things had begun to happen. Staff at Gresham College began telling people that Wessely had cancelled his lecture. However, other information indicated that Wessely was secretly going ahead. It was said that Wessely claimed he had reason to believe he would be physically attacked. Total confusion ensued, with people returning home believing that the lecture had been cancelled, when in reality it was going ahead. At the event, the police were present and were photographing everyone present. **The protest organisers had learned of Wessely's public appearance only a week before the event but, on the day, they managed to display personal stories of people whose lives had been destroyed by Wessely's ideas: some were harrowing, describing years of suffering, financial hardship, ridicule and abandonment by the NHS, family and friends as a result of Wessely's theories. The protest organisers believed that by ignoring *"the mountains of evidence about the physical causes of these syndromes, (Wessely) and his colleagues are personally responsible for suffering on a massive scale"*, so they had set up a campaign called "Illness Denied".**

On the day of the protest, the lead protester noticed unusual problems with her mobile phone. She also experienced problems with computer hacking (which in an official attempt to undermine her mental stability were ridiculed but which were later validated by an IT expert). The harassment included a threat placed on the internet directed at her children. She was subsequently arrested, with three police officers, two doctors, two social workers and a community psychiatric nurse arriving at her home unannounced with a warrant for her arrest. She was given no time to pack or to get in touch with a lawyer. She was then detained against her will under Section Two of the Mental Health Act 1983. She was kept on Pond Ward of the Central Middlesex Hospital for 30 days under appalling conditions. While she was under detention, her mother was suddenly taken ill and died a few days later; the protest organiser had to beg to be allowed out and was only permitted to see her mother accompanied by an escort in case she "escaped".

In her "Statement regarding my Detention", the protest organiser wrote: ***"I feel that my experience raises very serious issues about the powers that psychiatrists, social workers, and other authorities have in our society to repress others on the basis of their political beliefs***. *It is now clear that there are enough people out there who do have the courage to face issues even when they are controversial or call into question ideas we take for granted – that we live in a democracy, that public health authorities always act in our best interests, that governments are there to protect us, that psychiatrists in the west never diagnose and treat people on the basis of their political beliefs, that the science of medicine is never subordinated to politics or the profit needs of corporate giants. I believe that the recent events will only serve to focus people's minds more than ever on these issues".* The protest organiser was fortunate to have been supported by informed doctors, scientists, journalists, a peer of the realm and a very sharp, hard-hitting team of solicitors (http://web.archive.org/web/20070928204222/http://www.lyme-rage.info/elena/statejun06.html).

The above episode seems to have overtones of how Russia used to silence dissidents by giving them a psychiatric diagnosis and committing them to an institution, a situation that seems not to have disappeared in current times.

In The Daily Telegraph on 13th August 2007, Adrian Blomfield's article "Labelled mad for daring to criticise the Kremlin" told a harrowing tale of "punitive psychiatry" and referred to "state psychiatrists": "*The Daily Telegraph has learnt of dozens of incidents that suggest that Russia's psychiatric system is rapidly becoming as unsavoury as it was in Soviet times".* Blomfield wrote:" *'Once again psychiatrists see stubbornness in an individual as a sign of psychosis' said Lyubov Vinogradova, the executive director of the Independent Psychiatrists' Association.* ***'If a person goes to court against a state institution or writes letters of complaint he is treated as a social danger*** *and is in danger of incarceration' ".*

The same day, the following comments appeared on an ME internet group: ***"There is some parallel with the treatment of ME patients in the UK: (1) ME patients are given a psychiatric label. (2) As a result, they are regarded as irrational and their opinions are not taken seriously. (3) Effectively they are silenced, since no-one will afford them credibility. Not their GPs, not their MPs, not their employers, and sometimes not their friends. (4) By silencing patients, their opposition is neutered, and psychiatric dominance in ME continues unchallenged. (5) Liaison psychiatrists exult in their success, and bank their loot from the MRC and DWP"*** (see http://groups.yahoo.com/group/LocalME/).

As Greg Crowhurst, husband of an extremely severely affected ME sufferer, noted in his paper "Be a trouble maker": " ***'You can't go after a health care system (that is) under the control of the insurance companies and pharmaceutical corporations. That system is immune' warns Noam Chomsky in his latest book (Interventions; Hamish Hamilton, 2007), yet a radical corporate-led health care system is exactly what New Labour are bringing about in the UK, shadily and with little public consultation. Large companies are being invited to tender for the commissioning function of Primary Care Trusts (PCTs). Private companies will then have control over which treatments patients receive and who receives them. Clinical decision-making will increasingly come under the control of commercial managers and shareholders. That great bane of ME sufferers' lives, the medical insurance industry – which since the mid 1980s has lobbied hard with great success to have ME reclassified as a psychiatric behavioural disturbance, in order to avoid massive pay outs – makes no secret of its intention to take over the UK health market. In 2001, UnumProvident launched New Beginnings, a public-private partnership which has been hugely influential in shaping policy, especially in relation to the DWP's Pathways to Work programme. Illness, according to (Unum's) distorted logic, is a dysfunction of the person; the problem of illness is located in the individual's beliefs and behaviour.*** *New Labour's Welfare Reform Act was passed in May 2007. 'Pathways to Work', based on Unum's behaviourist logic, is to be rolled out across the country by 2008. GPs and Primary Care staff will be offered rewards for getting people back to work.* ***All of this is taking place against a wider picture of social control and state repression: as 'the new rulers of the world' (Pilger 2003), the corporations, aided and abetted by media and government, take over and implement health and social policies consistent with their own strategic and economic interests*** *(Noam Chomsky, Failed States, Penguin 2003). These topics however 'scarcely enter into public discussion and the basic facts are little known'. What can be done? It means a day-to-day dedication to the task. It means incredible courage and determination and above all a complete refusal to compromise on the truth that ME is a physical disease"* (Co-Cure ACT, 14th August 2007).

For more information, see "Corporate Collusion?" by Hooper, Marshall and Williams (http://www.meactionuk.org.uk/Corporate_Collusion_2.htm).

Interviewed on BBC Radio Ulster on 3rd May 2006, Jonathan Kerr, Senior Lecturer in Inflammation, Department of Cellular and Molecular Medicine, Hon. Consultant in Microbiology, St George's University of London, discussed his work on abnormal gene expression in ME/CFS and went on record stating: "***(ME)CFS is complex and it does involve many different systems…many of these patients are severely affected, so severely that they are bed bound and housebound for the duration of the illness, which may be lifelong…those that are not bed bound or housebound will have severe limitations in their professional capacity, their personal lives, their social life. So it is a very severe illness".***

The Medical Research Council's PACE Trial Principal Investigators, however, think that ME/CFS is an aberrant illness belief and that the behavioural modification strategies used in the PACE Trial are curative.

Patients with ME/CFS and their families are in despair, because no-one in authority in the UK seems to be listening: as Mike O'Brien MP, Minister of State for Health, made plain at the APPGME meeting on 2nd December 2009, Ministers can no longer tell agencies of State what to do. This apparently means that, no matter what conclusions are arrived at or what recommendations are made or what evidence is put before a Minister, the Minister concerned can deny having any power to implement change. The Minister himself is reported to have said that he could not require the MRC to undertake research in any specific field, nor

could he require Primary Care Trusts to follow Ministerial command. As far as ME/CFS is concerned, it seems that there is nothing the Government can -- or will – do about the current situation.

It is apparent that the Government feels no duty of care towards those whose life has been devastated by ME/CFS, a situation that is borne out by Professor Stephen Holgate's confirmation at the RSM Meeting on 11th July 2009 (Medicine and me; hearing the patients' voice) that the Government will not permit integrated research into ME/CFS.

This can only mean that the influence of the Wessely School over the lives of people with ME/CFS will continue and that their tactics of denial (see Appendix VII) will remain unchallenged, no matter what the calibre of the biomedical evidence showing them to be wrong. As people recently drily commented on an ME group, those tactics include:

"*load up your committees with your biased friends and pretend they are offering a fresh look; give really negative scorings to biomedical applications; try to stop biomedical papers getting published in the better known journals; make sure to keep on publishing psychiatric rubbish to bias the general medical population and scientific community against any other explanation, and give the impression that CBT/GET is all that is needed i.e. no need to waste all that money on silly biomedical projects"* (http://health.groups.yahoo.com/group/LocalME/ 6th December 2009) and *"ensure you use the sketchiest diagnostic criteria you can get away with; wherever possible, avoid seeing/talking to patients at all; never discuss/involve the severely affected; avoid using objective outcome measures; rotate the name of lead authors on papers and ensure you include plenty of reference papers from your psychosocial mates…."* (http://health.groups.yahoo.com/group/LocalME/ 7th December 2009).

As others have noted, the strategy is (1) to ignore ME; (2) to ensure that CFS is seen as a problem of false perception, then (3) to reclassify "CFS/ME" as a somatoform disorder (Co-Cure NOT:ACT: 12th January 2008), which is far removed from the reality of ME/CFS, the CNS dysfunctions of which are described by Dr Byron Hyde as being caused by "*widespread, measurable, diffuse micro-vasculitis affecting normal cell operation and maintenance….The evidence would suggest that ME is caused primarily by a diverse group of viral infections that have neurotropic characteristics and that appear to exert their influence primarily on the CNS arterial bed"* (ibid).

Patients and their families, many clinicians and researchers are well aware of such strategies and tactics but -- so powerfully has the Wessely School myth about ME/CFS been promulgated -- have been unable to halt them.

As Dr Jacob Teitelbaum reported, the XMRV virus study clearly documents that (ME)CFS is validated within the mainstream medical community as a real, physical and devastating illness, "*again proving that those who abuse patients by implying that the disease is all in their mind are being cruel and unscientific…Though the economics may cause a few insurance companies to continue to unethically deny the science, so they can avoid paying for the health care and disability costs they are responsible for, this research should speed up understanding of the illness. Meanwhile, for those with the illness, their families and their physicians, it is now clear that this is a real and devastating illness"* (Co-Cure RES: 4th December 2009).

That there is profound concern amongst parliamentarians about the psychosocial model of "CFS/ME" is recorded in the Minutes of the APPGME meeting that was held on 8th July 2009:

"***Chair*** (Dr Des Turner MP)**:** ***"I think that anyone who presumes to dictate a model of service for ME/CFS sufferers is being precocious, because there are no recognised guaranteed therapies. There are services which are offered but, as you know, they do not necessarily have any beneficial effect for sufferers, and in some cases, they can have adverse effects.*** *We are aware of that. That will be an issue covered by the inquiry"* (referring to the APPG Inquiry into NHS Service Provision for People with ME, which began taking evidence the following day).

"***Chair: We have consistently said in this group that, if we stand on one thing, it is that (ME/CFS) is a neurological condition – it is a biological condition, not a psychological condition***".

The Minutes also record concern (and the evidence) about the fact that NHS services that were in existence for ME/CFS patients have actually been replaced and the specialist doctors who were running those clinics have not been allowed to take part in the new "CFS" services.

As Jill Cooper from Worcestershire pointed out: "***There is no point in clamouring for more NHS resources if staff are being centrally 'trained' to view ME/CFS as a psychosomatic illness***".

The Minutes record that Sir Peter Spencer, CEO of Action for ME, referring to a meeting of the CNCC (Clinical Network Co-ordinating Centres that provide only CBT and GET for people with ME/CFS) at which he had been present, said: "*Professor Stephen Holgate gave…a very strong pitch based on his personal experience of* ***the frustration that ME patients have with the attitude towards the illness which was being taken by the people who are producing the current treatments***".

It was pointed out and minuted that to leave ME/CFS patients with no (appropriate) care is *"a breach of duty of care"*, a situation that is unlikely to change as a result of the MRC PACE Trial.

It is abhorrent that vulnerable and extremely sick patients should still be forced to justify their disease because of the ulterior motives of a group of influential psychiatrists who persistently dismiss the reality and severity of ME/CFS and upon whose diktat both State and insurance benefits necessary for basic survival are intentionally denied to those with ME/CFS.

This situation, however, seems to suit the UK Government nicely. Even an arch-ME agnostic such as Dr Theodore Dalrymple (pseudonym of psychiatrist Dr Anthony Daniels) wrote in his article "Spoiled for Choice" in the Daily Telegraph on 18th September 2009: *"When you go to your doctor, he is more likely to do what the Government has told him to do to – or for – you than what, as a professional, he thinks he should do".*

The sheer volume of illiteracy, misrepresentation, inconsistency and what appears to be frank misrepresentation to be found in the MRC PACE Trial literature is extremely disturbing to the extent that it appears to be little short of professional abuse of patients with ME/CFS, who for decades have rightly refused to accept the Wessely School's unproven and ill-informed dogma that ME/CFS is a behavioural disorder.

Regrettably, agencies of the State lack the patients' depth of knowledge and continue to be ensnared by the Wessely School's meticulously woven web of myths, which also seems to have contaminated the Judiciary.

As Sheila Campbell pointed out (MEAUK, 21st April 2009), Mr Justice Simon (the High Court Judge who heard the unsuccessful Judicial Review that set out to challenge the NICE Guideline on "CFS/ME") failed to differentiate between a belief and a scientific fact and drew his conclusions based on the false premise that he was dealing with two different points of view, when such was not the case – one is a belief, the other is supported by coherent and extensive medical and scientific evidence.
An opinion is a *"personal belief or judgment that is not founded on proof or certainty"* (http://tinyurl.com/cyy5k6).

A view is "*an expression of a belief that is held with confidence but not substantiated by positive knowledge or proof"* (http://tinyurl.com/c5xn32).

A fact is *"a concept whose truth can be proved"* (http://tinyurl.com/cq5ugk).

The Judge said: "*The 'psychosocial approach' describes the view that CFS/ME is a somatisation disorder, which needs to be recognised and treated as such"* (Introduction to Judgment, point 7). This is merely the Wessely School's belief: it is scientifically invalid.

The Judgment continued (Introduction, point 7): *"In contrast, the 'biomedical approach' describes a view that CFS/ME is an organic, neurological disease"*. That ME/CFS is an organic disease is not a "point of view", it is a fact, and is substantiated by a wealth of scientific evidence, including the International Classification of Diseases (ICD-10).

Mr Justice Simon repeated the fundamental error of stating that there are two "views" and seems to have drawn his conclusions and made his decisions based on the false premise that he was dealing with two differing points of view, which is not the case, thereby casting doubt on the whole Judgment.

The Judgment, however, served to perpetuate the Wessely School myth that ME does not exist.

Myths in medicine are dangerous.

In his article "How myths are made" (The Guardian; Bad Science, 8th August 2009), Dr Ben Goldacre shows how easy it is for medical myths to be created: he explains how the rejection of best practice can cut to the core of academia by distorting the facts: "*to understand the full damage that these distorted reviews can do, we need to understand a little about the structure of academic knowledge. In a formal academic paper, every claim is referenced to another academic paper"*, a practice that allows readers to *"trace who references what, and how, to see an entire belief system evolve from the original data"*.

Goldacre tells how an arbitrary hypothesis came to be wrongly transformed into "medical fact" by the frequent citation of just a few review papers, and how 95% of all citation paths flowed through just four review papers by the same research group, which focused citations on the few papers that supported the hypothesis.

Goldacre tells how Steven Greenberg from Harvard Medical School showed how these reviews "*exerted influence beyond their own individual readerships, and distorted the subsequent discourse"* and how *"through incremental mis-statement, in a chain of references, these papers came to be cited as if they proved the hypothesis as fact, which they did not.*

*"**This is the story of how myths and misapprehensions arise. Greenberg…found a web of systematic and self-reinforcing distortion, resulting in the creation of a myth, ultimately retarding our understanding of a disease and so harming patients**"*.

Comment 20 of numerous comments about Goldacre's article said: "***One has to wonder whether these people are consciously deceiving themselves or instead just have some peculiar mental block which prevents them from seeing any fact which fails to confirm their prior assumptions. (There is a third possibility that they are engaged in straightforward deceit**)"*
(http://www.badscience.net/2009/08/how-myths-are-made/#more-1309).

Many people – professionals and patients alike – wonder if this is precisely what has happened in relation to the Wessely School's studies on patients with "CFS/ME".

From the wealth of data obtained under the FOIA it seems inevitable that the Wessely School's myth that ME does not exist will be cast in concrete by the results of the MRC PACE Trial.

Using their own brand of magical medicine, it seems that they will finally have succeeded in making the disease ME disappear.

In his submission to the All Party Parliamentary Group Inquiry into NHS service provision for people with ME (Co-Cure ACT 1st October 2009), Tom Kindlon suggests that people with ME are being treated as second-class citizens:

"*The safety of treatments and interventions is one of the most important issues, if not the most important issue, in medicine. With many interventions such as pharmaceutical drugs, there are mechanisms in place so that if adverse reactions occur, this information is noted and attempts are made to collate the information…for example, (the) yellow card scheme, where either prescribing professionals or patients themselves can report adverse reactions. Unfortunately, with non-pharmaceutical interventions* (such as CBT/GET), *such options are not there. Currently, either the patient is blamed e.g. 'they did not do it correctly' or it is seen as the fault of the individual practitioner ('they did not do it properly'). Given there is no yellow card scheme* (for interventions such as CBT/GET), *what data do we have? The information from patient surveys is the obvious answer. It is important that professionals are told of the abnormal response to exercise in ME/CFS.* ***I do not see much evidence that professionals are being told of the abnormal response to exercise in ME/CFS patients****. It is also important that patients are given the risks associated with treatment. This does not seem to be occurring routinely at the moment. This means that patients cannot give informed consent to the treatments they are trying.* ***This suggests that people with ME/CFS are being treated like second-class citizens, not worthy of the protections that are offered to other patients. This needs to change****".*

It does indeed need to change, but it seems that some psychiatrists refuse to see themselves as the rest of the world sees them, or to see how history repeats itself through their own serious shortcomings. As Dr Derek Pheby, Director of the National CFS/ME Observatory, points out:

"…to assign someone to the wrong category on the basis of a false understanding of the nature of the illness and its context is an example of a well-known phenomenon which psychologists term 'fundamental attribution error' " (InterAction 2009:69:16-17).

It seems clear that the MRC is involved with a fundamental attribution error that, according to Dr Byron Hyde, is the error of our time (The Complexities of Diagnosis. In: Handbook of Chronic Fatigue Syndrome. Ed: Leonard A Jason et al. John Wiley & Sons Inc, 2003).

Many points emerging in this current document seem to bring not just the Wessely School but also the MRC itself into disrepute because they demonstrate how hollow is its alleged commitment to scientific rigour and its alleged requirement for *"high quality research"* and *"the high scientific standard required for funding"* (letter dated 15th April 2005 from Simon Burden of the MRC to Neil Brown).

There are some senior NHS Consultants who believe themselves to be infallible and who as a result harm large numbers of patients.

The MRC PACE Trial appears to be a textbook illustration on the successful purveying of misinformation and misrepresentation that foster a culture of animosity and contempt for ME/CFS patients which cannot but be detrimental to many very sick people.

Such animosity, disbelief and contempt towards people with ME/CFS is held by many people to be the legacy of the Wessely School: as noted above, patients with ME/CFS continue to be neither listened to, appropriately investigated nor correctly cared for but effectively abandoned, and the MRC PACE Trial appears to be part of that legacy.

As Christopher Cairns, father of a severely affected daughter, notes: *"what I worry about more is the disbelief factor, which only guarantees years of deep and unabiding misery"* (http://cfspatientadvocate.blogspot.com/).

It is time for the Wessely School's legacy to be over-turned, for this complex disorder to be recognised as the devastating condition that it is, and for those blighted by it to get the treatment, help and support that

they so desperately need and deserve and which is afforded to patients with other serious illnesses as a matter of course.

Carried out by the Wessely School themselves, the MRC PACE Trial, however, is likely to ensure that -- suicide apart -- sufferers of ME/CFS will be offered only inappropriate and potentially harmful psychotherapy and so will have no option but to continue unsupported to endure their ruined lives.

Neither the UK Government nor the medical / permanent health insurance industry is likely to care.

However, to quote US ME/CFS sufferer and advocate John Herd:

"*With the advent of the Whittemore-Peterson Institute's XMRV research we may be entering a new and more relevant era of research for our illness. So will it put the medical fantasies about the illness to rest? What of the likes of Simon Wessely and Michael Sharpe who have both created and perpetuated those fantasies under the guise of supposed science?* ***For decades the psychiatric profession has been increasingly trying to elevate itself by portraying psychiatry as pure science. What happens now that Simon Wessely's and Michael Sharpe's theories about ME/CFS are being scientifically proven to be nothing more than tainted data conducted and created to support preconceived flawed theories?*** *What does the psychiatric research sector do now that it is becoming evident that two of their own have corrupted 'the science' so profoundly? Do the psychiatric sector, academic medical sector and government health sector distance themselves from such corruptions of science? That is usually what happens when an investigator is shown to have been generating corrupted data. Or will (they) rally around to protect their own, making the whole matter more scientifically reprehensible?* ***As we enter this new era of ME/CFS research it is not enough to let the gradual process of science illuminate the contradictory nature of Simon Wessely's and Michael Sharpe's decades-long campaigns. We advocates must bring the contradictions to the doorsteps of psychiatric research, academic medical, government health and media sectors. If we do so effectively, we can open the doors to more needed research in the days and months ahead***" (Co-Cure ACT, MED, NOT, RES: Will dominoes fall? 26th October 2009).

This will be difficult: eighteen years after the 1992 CIBA Symposium on CFS, members of the Wessely axis are still promoting their agenda identified in the secret MRC document referred to above.

For example, in a 2008 paper comparing "chronic fatigue" in Brazil and Britain, Cho and Wessely et al could not have been more explicit: "*British patients were more likely to be a member of a self-help group and to have had sick leave / sickness benefit because of CFS, variables claimed to predict poor outcome…****The greater public and medical sanctioning of CFS/ME and the more favourable economic climate in the UK may lead to greater access to sick leave / benefits for patients with chronic fatigue….There is also evidence of an association between the so-called 'secondary gain' and health outcomes….Therefore, the higher availability of sick leave / sickness benefit because of CFS in the UK may both contribute to and reflect the greater 'legitimisation' of chronic fatigue as a medical disorder***" (Physical or psychological? A comparative study of causal attribution for chronic fatigue in Brazilian and British primary care patients. Acta Psychiatr Scand 2008:1-8).

Reid noted how the article reflected the MRC-funded PACE Trial of CBT and GET as set out in the Trial Protocol that was published in BMC Neurology (2007:7:6): "*Predictors of outcome: Predictors of a negative response to treatment found in previous studies include…membership of a self-help group, being in receipt of a disability pension, focusing on physical symptoms and pervasive inactivity*" (3,18,19) (http://www.meactionuk.org.uk/Wessely-axis.htm).

There is no mention in that paper of on-going viral infection but, perhaps expediently, in a paper that came out about the same time as the XMRV news broke, Wessely quietly inserts his own new model that allows for infection as a perpetuating factor, so the Wessely School goal-posts may be subtly shifting: "*…a model of the aetiology of CFS can be constructed from a combination of pre-morbid risk, followed by an acute event leading to fatigue, and then a pattern of behavioural and biological responses contributing to a prolonged severe fatigue syndrome.*

*Based on this model, the initial cause of the fatigue has a limited impact on the eventual course of the illness….**However, there is emerging evidence which suggests that it may be appropriate to extend it to encompass fatigue with an apparent medical cause….it may be that the divide between fatigue secondary to diagnosed medical problems and CFS may need to be made more permeable**"* (Chronic fatigue syndrome: identifying zebras among the horses. Samuel B Harvey and Simon Wessely. BMC Medicine 2009:7:58).

This is very different from the PACE Trial concept of "CFS/ME" which, in over 2,000 pages of information obtained under the Freedom of Information Act, including all the Manuals, does not allow for any on-going pathology.

Because ME/CFS is known to be a targeted disorder for the withdrawal of state benefits, the situation for ME/CFS patients in the UK is increasingly dire, with severely affected patients being harassed by the Department for Work and Pensions requiring a 60-page booklet to be completed because the DWP menacingly informs such patients: *"We have reason to believe that you are capable of work".*

An article entitled "Mistaken Illness Beliefs…" by David Lees published in the ME Association's magazine "ME Essential" (Winter 2009: 34-35) exactly captures the situation:

*"…a friend with ME…was told, despite the persistence of her symptoms, that the only thing preventing her full recovery was her 'mistaken illness beliefs'…'But doctor, I still have nausea / muscle pain / severe weakness / headaches / exhaustion etc' can all be met with 'It's just your illness beliefs. There's nothing else wrong, and if you still experience symptoms, it's because you haven't got your beliefs right yet. As soon as you do, you'll be well'….It's impregnably self-immunised (*referring to Sir Karl Popper's 'self-immunisation' theory which showed that such theories are scientifically worthless because they have no real explanatory or predictive power) *and therefore scientifically worthless as a diagnosis……*(Referring to researchers who are struggling to uncover complex mechanisms and to answer difficult and involved questions, Lees continues): *Uncertainty and humility are appropriate attributes in these circumstances and they seem noticeably lacking in much of the psychological approach to diagnosis and treatment of ME**…..Doctors are presented with difficult, confused, uncertain data and interpretation can be very difficult; but surely this is an argument for more caution and admissions of uncertainty rather than a reason to make scientifically dubious statements with Olympian self-certainty…In the absence of proper research evidence, to work from the assumption that the illness is not primarily organic in origin and must therefore be primarily psychological is unscientific…We should surely have moved on from filling gaps in our medical knowledge with assertions…the least we should expect from medical practitioners in the NHS, whose diagnosis profoundly affects the lives of those with ME, is that their methods and conclusions should be scientific. The diagnosis of 'mistaken illness beliefs' is not – it is itself merely a statement of belief".***

Given the significant opposition to the PACE Trial from many quarters, including both patients and professionals and also including the ME Association (the oldest ME charity) and, it is understood, from many patient members of the charity Action for ME (though not the charity's Trustees, who support the PACE Trial, which seems to indicate that AfME is not a patient-led organisation), there are compelling grounds for suggesting that the PACE Trial should never have been granted approval or funding.

As noted above, the ME Association had called for a stop to the PACE and FINE Trials; the Report of the PACE Trial statistician Dr Tony Johnson (a member of the Trial Management Group, a member of the Trial Steering Committee and the person who will oversee the Clinical Trial Unit that is directed by Professor Wessely) confirmed in the MRC's Biostatistical Unit's Quinquennial Report for 2002 – 2006 that the MRC was funding the PACE and FINE Trial *"despite active campaigns to halt them"* (a notable point is that his Report was co-authored by Professors Peter White, Trudie Chalder and Michael Sharpe, so all of them were aware of the strength of opposition to the PACE Trial), and Principal Investigator Professor Michael Sharpe also confirmed: "*The MRC is currently funding the PACE trial….However, the trial has faced serious antagonism from some, but not all, patient groups, mainly because of concerns about the use of 'psychological treatment' for a*

condition that is seen by many as a medical disorder" (Report on MRC Neuroethics Workshop, 6th January 2005: Section 2: Altering the brain).

It is certainly the case that even the MRC's own Neuroethics Committee expressed doubts over the use of CBT: *"…CBT aims to influence how a person thinks or behaves…Although psychotherapies are usually thought of as psychological therapies, there is increasing evidence that they can alter brain function.* ***Further research is needed to …determine whether therapies are reversible or if there are persistent adverse effects.*** *There is already evidence that in certain situations psychotherapy can do harm…****There is also increasing public concern that psychological therapies could be used for brainwashing****….How much information should patients be given about the possible effects of therapy on their brain?….CBT techniques are now being used more widely to treat somatic conditions…How appropriate is this use of psychological therapy?*

How, for instance, does the Wessely School's "CBT model of CFS" accord with the fact that in the South African epidemic, all the rats that were injected with the urine of ME patients died, but not a single rat died that was injected with the urine of controls? The Wessely School's answer is likely to be that "epidemic ME" is not the same as present day "CFS/ME", an explanation that does not withstand scrutiny, given that the only symptoms of "CFS/ME" on which the Wessely School focus are those that are known to occur in mental disorders (tiredness, anxiety, depression and mood disorders, the latter being a consequence, not a cause, of ME/CFS), whilst ignoring, dismissing or wrongly attributing symptoms such as vertigo, post-exertional physiological exhaustion, intractable pain, neuromuscular in-coordination and dysautonomia to "*hypervigilance"* to "*normal bodily sensations",* a situation best described as iatrogenic abuse.

As clinical psychologist Carl Graham recently pointed out, the type of CBT "***used in psychoneuroimmunological interventions is not limited to changing 'irrational beliefs' '",*** noting: "***The view that all those involved with CBT based treatments accept the idea that irrational thinking had led to a somatoform disorder in a patient who has a chronic disease is entirely unfortunate"*** (Co-Cure NOT 14th December 2009) and in an update (Co-Cure 15th December 2009) the same psychologist referred to *"the association of CBT with the very unfortunate tendency of some in the treatment field to claim ME/CFS is a somatoform or psychiatric disorder"*, concluding that he was *"not advocating for CBT based practices for chronic health problems to continue where they are being done poorly or as a monotherapy".*

To change what they regard as "*irrational beliefs"* of people with "CFS/ME is, however, the expressed intention of the PACE Trial Investigators, who continue to promote CBT/GET as a monotherapy for "CFS/ME", a matter of concern to experts such as Dr David Bell from the US, who on 12th December 2009 was quoted in The Daily News online: "'*The tiredness linked to (ME)CFS is caused by a reduction of blood flow to the brain' Bell said. The doctor said the blood flow in people with severe cases of (ME)CFS can be as low as people with terminal heart disease".* Would people with terminal heart disease be required to undergo psychotherapy to convince them they are not in fact sick, but only <u>believe</u> that they are sick?

The apparent intention of the PACE Trial Principal Investigators to remove people with ME/CFS from receipt of state and insurance benefits raises a larger question than just welfare reform. It is also about the way illness is being redefined and reclassified and about why this is happening and about what forces are at work in this process of redefinition.

As noted by Overton (Psychological Medicine 2010:40:172-173; online 08.10.09), in Sharpe et al's 2009 study referred to above ("Neurology out-patients with symptoms unexplained by disease: illness beliefs and financial benefits predict one-year outcome"), one of the authors (Stone) accepts that terms such as 'functional weakness' may well need to be re-worded as 'conversion disorder' on official documents. Challenging Sharpe's assertion that their data lend *"support to the idea that interventions which change these variables [ie. state benefits or opposition to physician-imposed psychological explanations of physical symptoms] may improve the outcome for this patient group"*, Overton points out that Sharpe et al inadvertently infer that patients with *"symptoms unexplained by disease"* are guilty of benefit fraud and Overton states that it is erroneous for Sharpe to use data in the way he does to assert that *"Illness beliefs and financial benefits are more*

useful in predicting poor outcome than the number of symptoms, disability and distress". Moreover, Sharpe's assertion contrasts with the evidence of Rosata & Reilly who, unlike Sharpe, correlate the level of benefit with the degree of disability (Health & Social Care in the Community 2006:14:294-301).

In their Editorial in the Journal of Psychosomatic Research (Is there a better term than 'Medically unexplained symptoms?' 2010:68:5-8, Epub ahead of print), two of the MRC PACE Trial Principal Investigators, Professors Sharpe and White, clearly state their intention to claim medically unexplained symptoms (MUS -- in which they include ME/CFS) as psychosomatic disorders by stating that the term "*functional somatic disorder"* fulfils most of their own criteria for re-branding somatoform disorders (those categories being "*bodily distress or stress syndrome*", "*psychosomatic or psychophysical disorder*", and "*functional syndrome or disorder*"). Sharpe and White et al continue: "***All too often, these patients receive one-sided, mostly purely biomedical…treatments….Although some existing treatment facilities include both biomedical and psychological therapies…they are not appropriate for …the majority of patients with the type of symptoms with which we are concerned here. Therefore, some specific treatment facilities have been developed (eg. Chronic Fatigue Clinics in the UK)****….The terms…'psychosomatic' or 'psychophysical' are helpful in providing a positive explanation of the symptoms…Alternatively, the term 'functional somatic syndrome' allows explanations…in terms of altered brain functioning…demonstrating that the symptoms are 'real' and yet changeable by alteration in thinking and behaviour as well as by a psychotropic drug****".*

There could be no clearer confirmation that the UK "CFS" Clinics allegedly for patients with ME/CFS that were set up under the guidance of Professor Anthony Pinching were and remain intended to change patients' thinking and behaviour, which vindicates the countless patients whose damaging experiences and legitimate concerns have been collated by Research into ME (RiME NHS Clinics Folder -- www.erythos.com/RiME).

In an article in the New York Times that was published before the PACE Trial began (27th August 2002: "Behaviour: Like Drugs, Talk Therapy Can Change Brain Chemistry"), Richard Friedman MD — a psychiatrist who directs the Psychopharmacology Clinic at the New York Weill Cornell Medical Centre – stated "*Psychotherapy alone has been largely ineffective for diseases where there is strong evidence of structural, as well as functional, brain abnormalities.* ***It seems that if the brain is severely disordered, then talk therapy cannot alter it***".

As there are structural brain abnormalities documented in the ME/CFS literature since at least 1992 (see Section 2 above), one of which being the significant loss of grey matter in the brain with irreversible loss of grey cells, especially in Brodmann's area 9, (which may indicate major trauma to the brain), then the chance of cognitive behavioural therapy being effective in ME/CFS is probably zero.

Indeed, it was reported by Professor Leonard Jason at the Reno Conference that one group of patients did not benefit from cognitive behavioural interventions: this was the subset whose laboratory investigations showed they had increased immune dysfunction and low cortisol levels.

As the data discussed by Friedman was known about in 2002 (the same year that the UK CMO's Working Group Report was published), it must be asked why this knowledge has been disregarded by the Wessely School psychiatric lobby, especially given that they knew in 2003 – from their own research – that people who responded to CBT had baseline urinary cortisol levels close to normal, whereas those who did not respond had baseline levels below normal (quoted by Jason LA, Fletcher MA et al. Tropical Medicine and Health 2008:36:23-32) and that *"those who were most impaired on HPA functioning might have been the least able to improve with graded activity interventions"* (paper presented by Anthony J Cleare at the meeting towards understanding the cellular and molecular mechanisms of medically unexplained fatigue, 2003: Cold Spring Harbor Laboratory, New York).

As pointed out by Tom Kindlon (Co-Cure ACT: 7th January 2010), although known about in 2003, this finding was not published until 2009 (Roberts AD, Wessely S, Chalder T, Cleare AJ et al. Psychol Med 2009:

17th July: 1-8 (Epub ahead of print) despite the fact that another part of that study was published in 2004 (British Journal of Psychiatry 2004:184:136-141).

As Kindlon notes, if the knowledge that the efficacy of CBT/GET might depend on cortisol levels, had this knowledge been made public prior to publication of the NICE Guideline in 2007, then the Guideline could not have "sold" CBT/GET as being suitable for all patients with "CFS/ME".

Given what is already known about the inherent dangers of CBT/GET for those with ME/CFS (especially the known effects of graded exercise as an inducer of oxidative stress and the effects of incremental aerobic exercise on the cardiovascular problems known from the early part of the twentieth century to be an integral feature of authentic ME/CFS), on what ethical grounds can those already crushed by such a heavy illness burden as that imposed by ME/CFS be subjected --- despite denials, in some cases by misinformation and coercion – to a management regime that seems to have no hope of beneficial results?

On 10th January 2010 the BBC's World Service broadcast a programme "Animals and Us" (One Planet, 02.30 – 03.00) in which Professor Lowell Levin, Professor Emeritus and Lecturer at Yale University's School of Public Health (who also serves as a senior consultant to the WHO) was forceful: he said that the pharmaceutical and associated industries make money from keeping myths going and that they make *"profits of a magnitude hard to conceptualise"*.

He was clear: ***"There's too much money to be made in falsifying the causes and the cures"***.

This raises once again the disturbing question: in whose best interests is the MRC PACE Trial being undertaken?

SECTION 4: QUOTATIONS FROM THE MRC PACE TRIAL MANUALS

General observations on the PACE Trial Manuals and Leaflets

The most striking impression is that the Manuals are ill-written, often grammatically incorrect, lacking in intellectual rigour and internally inconsistent.

They are also carelessly written: for example, a "medical specialist" in one sentence suddenly becomes a "therapist" in the next.

Although the Minutes of the Joint Trial Steering Committee and the Data Monitoring and Ethics Committee meeting that was held on 27th September 2004 record: "*Professor Darbyshire noted that the term CFS/ME has not been used consistently",* the disease is variously referred to as "chronic fatigue", "chronic fatigue syndrome", "CFS", "ME", "Myalgic Encephalomyelitis", "Myalgic Encephalitis" or as "Myalgic Encephalopathy", hence despite Professor Darbyshire's concerns, these inconsistencies remain uncorrected.

It appears that there is nothing in the Manuals that approaches either medical science or logic, or indicates that the authors have any understanding of the true nature of the neuroimmune disease ME/CFS.

Speculation is portrayed as fact. Assumptions are portrayed as "evidence".

For example, on page 17 in the CBT Therapists' Manual the authors say: "*There is a growing body of evidence that is suggesting that a number of factors may be involved in triggering the illness",* but on page 18 this becomes: *"Just as there are many factors involved in triggering CFS/ME, there are also many factors that are involved in sustaining it"* -- so a "suggestion" that "a number of factors" are involved in triggering "CFS/ME" has become an established fact, despite being unproven.

Given the existing published evidence-base about ME/CFS, how such a Trial was approved by any Ethics Committee is bewildering.

The significance of a particular comment in a Manual cannot be captured without reading the full Manual and by cross-referencing with other Manuals in order to discover the many contradictory and unsubstantiated statements.

It could be argued that participants were not in a position to give fully informed consent to the interventions described in the Manuals (for example, participants in both the CBT arm and the GET arm of the Trial were to be treated as though they had no physical disease, but this important fact was withheld from them).

It is notable in this respect that Lord (David) Sainsbury of Turville, who at the time was responsible for the MRC, stated in the House of Lords: *"Because the trial participants will have provided informed consent, they will receive no compensation if they become more ill, whether or not as a result of the particular treatment*" (Hansard [Lords]: 18th November 2004: 4830) and participants were to be informed that: "*we don't expect to see any harmful effects caused by our study. However, you need to know that there are no special compensation arrangements if you are harmed because you have taken part"* (SSMC Participant Information Sheet for PACE Trial).

The Manuals are full of contradictory claims – for example, the CBT Manual for Therapists states that they are treating some participants *"who generally do too much",* which entirely vitiates the premise upon which the whole PACE Trial is based, ie."*the illness model of both deconditioning and exercise avoidance*", since it is obvious that people who generally do too much do not suffer from exercise phobia and cannot be deconditioned.

The APT Manual for Participants advises them that: "*Recreational activities are what you may have previously described as relaxation…for example, going to the pub after a busy day at work. Recreational activities* (such as going to the pub) *need to be reintroduced as part of your programme of rest and activity"*, yet this particular recommendation is advised against in the Participants' CBT and GET Manuals: "*alcohol…can affect sleep by making it difficult to go to sleep"* (CBT Participants' Manual, page 28); *"Most people with CFS/ME will avoid or take little alcohol due to them* (sic) *exacerbating their symptoms"* (CBT Therapists' Manual, page 42); *"We know that it is unusual for people with CFS/ME to drink much alcohol"* (GET Participants' Manual, page 62).

The message for participants about alcohol is therefore dependent upon the arm of the trial to which they have been randomised: APT participants are encouraged to drink but CBT and GET participants are advised to avoid drinking.

There seems to be the clear intention running through all the Manuals to regard "CFS/ME" as neurasthenia, which is the Wessely's School's long-held conviction.

In 1991, John Wiley & Sons published "Post-Viral Fatigue Syndrome" edited by Rachel Jenkins and James Mowbray; in her own contribution, Professor Jenkins, a Principal Medical Officer at the Department of Health and currently Director of the WHO Collaborating Centre for Mental Health at the Institute of Psychiatry, made it clear on page 242 that there is no anhedonia (loss of any pleasure/interest in life) in ME.

However, in his official role as Parliamentary Under Secretary of State for Health / Community Care, Dr Stephen Ladyman MP went on record on 28th July 2003 stating that the WHO was initially *"eager"* to refer to CFS/ME in the Guide to Mental Health in Primary Care as ***"neurasthenia"***, but that it was eventually decided to call it *"chronic fatigue syndrome (may be referred to as ME)".* It will be recalled that the WHO has confirmed that it has no intention to re-classify to ME/CFS as neurasthenia.

The cardinal feature of neurasthenia is **anhedonia**, yet Professor Jenkins is on published record as stating that there is **no** anhedonia in ME.

To which disorder are the PACE Trial Manuals referring? It cannot be ME/CFS because the entry criteria for the PACE Trial (the Wessely School's own Oxford criteria) exclude those with neurological disorders. It is, in fact, "CFS/ME", which the Wessely School regard as a behavioural disorder (chronic "fatigue" or neurasthenia).

Once the Trial's many internal inconsistencies become known, the validity of the whole Trial comes under suspicion, and consequently the results may not be relied upon.

Background to some of the authors of the PACE Trial Manuals

Before continuing, it should be borne in mind that the same people who wrote the CBT Manuals for the PACE Trial (Mary Burgess and Trudie Chalder) wrote the book "Overcoming Chronic Fatigue" (February 2004, ISBN 9781841199429), some background to which may be helpful.

Although the title refers to "Chronic Fatigue", the book addresses Chronic Fatigue Syndrome: *"Chronic Fatigue Syndrome is a debilitating illness…..Via recognised CBT techniques that change our attitudes and coping strategies, this approach is successful in breaking the cycle of fatigue, with a reduction in symptoms and disability in up to two thirds of sufferers".*

The authors state about the trials upon which they rely in their book: "*The effectiveness of CBT in treating CFS has been evaluated in three well-conducted research studies undertaken since the 1990s. All three were conducted as randomised controlled trials; that is, trials in which there are more than one treatment group,* ***and participating***

***patients do not know which group they are in**. CBT was found to produce better results than the other treatments with which they were compared".*

The trials mentioned by Burgess and Chalder are the same trials upon which the PACE Trial Principal Investigators relied for justification of the trial, all of which have been shown to have serious methodological flaws (S Butler, T Chalder, M Ron, S Wessely, JNNP 1991:54:153-158; Sharpe M et al, BMJ 1996:312:22-26; Deale A, Chalder T, Marks I, Wessely S, Am J Psychiat 1997:154:3:408-414).

On 6th January 2006 a severely affected ME sufferer wrote to Dr Burgess about the three trials referred to in their book: *"I can well understand that it must be crucially important that participating patients do not know which group they are in, and I am wondering if you can tell me how that was achieved in the three trials you refer to?"*

When the error in their book (ie. that in the three trials in question, *"participating patients do not know which group they are in")* was brought to her attention, on 9th January 2006 Dr Burgess' reply was notable: ***"The paragraph to which you refer is a mistake that I had unfortunately not noticed before it went to print. Patients did know the group to which they had been allocated** because they would have had to know about the different treatments before consenting to the trial".*

That was a remarkable mistake not to have noticed.

When the same person wrote again to Dr Burgess enquiring if there had been any critical commentaries about the three trials relied upon in their book, the enquiry was ignored.

It was in fact the case that numerous criticisms of those studies existed. For example, Friedberg and Jason's book "Understanding Chronic Fatigue Syndrome" (American Psychological Association, 1998) was explicit about two of the three studies that underpinned the Burgess and Chalder book (Deale A, Wessely S et al 1997 and Sharpe et al 1996):

"It is possible that psychiatric morbidity rather than a CFS disease process maintained disability and symptoms status…a near-complete resolution of the illness, as reported in Sharpe et al (1996) suggests the presence in many patients of primary psychiatric illness with prominent fatigue symptoms, rather than CFS".

"The heterogeneity of the CFS population may be another factor that is related to clinical outcome".

"…patients…showed a high degree of psychiatric morbidity".

Further criticisms had been noted by others: in the Deale and Wessely et al study of 60 patients, half received CBT in the form of *"graded activity and cognitive restructuring"* and half received "*relaxation*". Three subjects withdrew from the CBT group and four withdrew from the relaxation group. No details were given by the authors of any symptoms apart from "fatigue". Half the participants did not think that they had a physical illness; there was about a seven year age gap between the two groups (the CBT group being the younger group); it seems that there were no proper controls; there was no placebo arm and no non-treatment arm (both required); there was no blinding; there were no independent assessors; and it was the same individual therapist on both arms of the trial. The authors stated that at final follow-up (six months after the course of CBT and relaxation was completed), 19 patients *"achieved good outcomes compared with 5 patients in the relaxation group".* **Somatisation disorder and severe depression were cited as exclusion criteria, yet nine participants were described as having 'major depression' and there were high levels of existing psychiatric morbidity in the study cohort.**

Outcome measures were said to relate to "*subjectively experienced fatigue and mood disturbance, which are the areas of interest in chronic fatigue syndrome*". This statement alone indicates that the study cannot have been considering people with ME/CFS because neither "fatigue" nor mood disturbance is a

defining feature of ME/CFS (the defining feature of ME/CFS being post-exertional muscle fatigability with malaise).

Of concern is the fact that the authors stated: "*The aim was to show patients that activity could be increased steadily and safely without exacerbating symptoms*". That is a remarkable statement. It demonstrates that the authors had decided -- in advance of the outcome -- that activity could be increased without exacerbating symptoms. This was not merely the authors' hypothesis: that this would be the outcome was taken for granted.

Of note is the fact that the outcome did not meet the authors' certainty, and the authors had to concede that: "*cognitive behaviour therapy was not uniformly effective: a proportion of patients remained fatigued and symptomatic*". Perhaps for this reason, the presentation of results was mostly reported as averages, rather than giving actual numbers of patients. The authors acknowledged that: "*The data from all the outcome measures were skewed and not normally distributed, with varying distributions at each measurement point*". In such circumstances, merely providing "average" figures is not the most appropriate illustration of findings. In summary, this RCT has little relevance in general and none whatever to people with ME/CFS.

Burgess and Chalder's informing members of the public who bought their book that the trials they cited were double blind when they were not even single blind, and their reliance on studies that were shown to be flawed, demonstrates a worrying and evident failure to understand the most elementary tenets of the scientific process.

These same people are, however, the authors of the MRC PACE Trial Manuals on CBT for both therapists and participants, which sadly are also replete with misinformation.

There are seven Manuals for the PACE Trial; these are:

The Therapists' Manual for Cognitive Behaviour Therapy (CBT) is written by Mary Burgess and Trudie Chalder. It is entitled: "Manual for Therapists. Cognitive Behaviour Therapy for CFS/ME". Acknowledgements are made to Jessica Bavinton, Diane Cox, Vincent Deary, Michael Sharpe, Bella Stensnas, Sue Wilkins, Giselle Withers and Peter White.

The Therapists' Manual for Graded Exercise Therapy (GET) is written by Jessica Bavinton, Lucy Darbishire and Peter White and is entitled "Manual for Therapists. Graded Exercise Therapy for CFS/ME". (Dr Lucy Darbishire – now Dr Lucy Clark – an exercise scientist from King's College, London, believes that CFS is *"just another end of the spectrum [of fatigue]"* – Brit J Gen Practice 2003:53:441-445). She is not to be confused with Professor Janet Darbyshire, Chair of the PACE Trial Steering Committee. Acknowledgements are made, amongst others, to Mary Burgess, Diane Cox, Trudie Chalder, Kathy Fulcher, Gabrielle Murphy, Pauline Powell and Michael Sharpe. Contributions from (un-named) members of the Trial Steering Committee, the Data Monitoring and Ethics Committee and the Trial Management Group are also acknowledged.

The Therapists' Manual for Adaptive Pacing Therapy is entitled "Adaptive Pacing Therapy (APT) for CFS/ME" and is written by Diane Cox, Sally Ludlum, Louise Mason, Sally Wagner and Michael Sharpe. Acknowledgements for their invaluable contribution are made to Mary Burgess, Jessica Bavinton, Vincent Deary, Trudie Chalder and Peter White.

The Manual for Standardised Specialist Medical Care ("SSMC") is entitled "Manual for Doctors. Standardised Specialist Medical Care (SSMC)" and is written by Gabrielle Murphy, David Wilks, Michael Sharpe, Mary Burgess and Trudie Chalder.

The Participants' Manual for CBT is written by Mary Burgess and Trudie Chalder.

The Participants' Manual for GET is written by Jessica Bavinton, Nicola Dyer and Peter White.

The Participants' Manual for APT is written by the same authors who wrote the APT Manual for Therapists.

The Therapists' Manuals for CBT (page 5), GET (page 11) and APT (page 8) all inform the various therapists that there is controversy about whether CFS, PVFS and ME are identical conditions. This is incorrect -- the WHO considers them to be the same neurological disease. There is no controversy except the controversy created by the Wessely School themselves, who do not accept that ME/CFS is a neurological disease and who have created their own disorder "CFS/ME", which is a behavioural disorder. It is vital to understand that when the Manuals state *"we will consider them together here as CFS/ME"*, although claiming to include patients with ME, they are not referring to ICD-10 G93.3 (ME/CFS/PVFS) but to ICD-10 F48.0 (ie. as a unified behavioural disorder).

The "Summary of Therapies" in the Therapists' Manuals and in the SSMC Manual describes APT as "*simple, non-incremental pacing*"; CBT as "*complex incremental pacing*", and GET as "*simple incremental pacing*".

In the table "*Distinguishing between APT, CBT and GET"*, it is stated in all the Therapists' Manuals that **CBT and GET do not work from a pathological assumption but from a deconditioning assumption**. This is an unambiguous statement that the PIs believe that ME/CFS should be treated as though it is not a physical disease, and it confirms that the MRC and DWP (with the support of Action for ME) are funding research based on the conviction that is is a mental health problem.

However, page 43 of the Full Trial Protocol states: "*APT will be based on the illness model of CFS/ME as a currently undetermined organic disease".*

APT may not be the same "pacing" as patients have always understood it (ie. practical common sense, which cannot be turned into a "therapy" because it concerns the intelligent self-regulation of activity from personal experience). Pacing is an innate survival instinct; no-one invented it – it evolved as a means of conserving sufficient energy to meet metabolic demands and is thus health-protective, not "*maladaptive behaviour*" as the Wessely School assert. Advising sick people not to heed this survival instinct -- ie. not to rest when rest is essential -- is potentially dangerous.

The APT Therapists' Manual states on page 19: "*The pacing therapy used in this trial is based on that reported as useful by people with CFS/ME and collated by the patient organisation Action for ME (AfME 2002, 2003)".*

However, the Chief Medical Officer's Working Group Report of 2002 relied on the definition of pacing included in the UK National Task Force Report on CFS/PVFS/ME (Westcare, 1994), where it is described as: "*Getting the right balance between rest and exercise…(This) will vary not only between individuals but also in the same individual over the course of time…**The simplest way of finding the 'right' level of activity is to LISTEN TO YOUR BODY and do no more on a good day than you can manage on a bad day***" (Section 14.3 – 14.3.2, page 66-67).

PACE Trial participants and therapists alike may be misled about APT being the same as pacing: the Trial literature states *"APT…has been recommended by a recent Government working party as one of the treatments of choice for CFS/ME"*; however, contrary to the pacing recommended in the CMO's Report that patients with ME/CFS find helpful, APT requires planned activity.

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 "doing what you can when you can".

Merely calling the application of common sense a "treatment" does not make it one.

In summary, the PACE Trial version of "pacing" (APT) requires homework and practice and includes planned relaxation and activity, practised regularly and consistently (ie. to a timetable) and the use of daily diaries in which participants must analyse their own activities. Participants must undertake breathing exercises and APT involves its own targets and methods. Its aim is that the participants do not remain at a fixed activity level.

Referring to APT as "pacing" seems designed simply to offer a false sense of security in order to get patients "on side".

The Manuals for PACE Trial therapists and for doctors emphasise the need for "*positive reinforcement"* throughout; each Manual drives home the message: "*It is essential that you demonstrate positive reinforcement"* and *"Every session you should positively reinforce all of their achievements, however small they may seem".*

It appears that the interventions must be assiduously "sold" to the participants, who must be encouraged to stay in the trial at all costs.

This accords with what Peter White submitted to NICE in the St Bartholomew's Stakeholder comments (1.3.1.6, in which he denied that "CFS/ME" is an incurable chronic disease): ***"The expectation of both the patient and the practitioner is vitally important in determining outcome"***.

Despite the publicly available evidence to the contrary of the experience of people with ME/CFS (referenced in Section 1 above), therapists are told that CBT/GET are "*safe and effective treatments"* for participants.

The SSMC Manual defines SSMC as non-specific advice about balancing rest and activity and says that *"SSMC includes communication with and sharing of care with the participants General Practitioner*", which hardly constitutes "Standardised **Specialist Medical Care**".

A theme that emerges very clearly from the Manuals is the frequent ambiguity of language. For example, the CBT Manual for Therapists states on page 18: "*According to this model, the symptoms and disability of CFS/ME are perpetuated predominantly by unhelpful illness beliefs (fears) and coping behaviours (avoidance)"*. By using the word "predominantly", the authors recognise that their model is incomplete, yet on page 21 this uncertainty has disappeared and the same Manual confidently asserts: "*Treatment is focused on addressing the cognitive and behavioural factors that maintain the vicious circle of CFS/ME"*.

There is no evidence that ME/CFS is a "*vicious circle*", or that "*cognitive and behavioural factors*" maintain it.

Using quasi-scientific language, the authors of the PACE Trial Manuals have authoritatively projected their assumptions as proven facts.

This might lead participants to believe that, as "experts", the Investigators and therapists are working from established scientific and medical principles.

This is in contradiction to the theoretical nature of the investigations being tested, ie. the Manuals do not make clear that it is the validity of these theories that is being tested in the PACE Trial and that the assertions in the Manuals have not been proven.

The PACE Trial literature is telling participants that Investigators and therapists know that what they are saying is correct, when such is not the case, a situation that many people deem to be unacceptable.

In 1997, Michael Sharpe published his concept of cognitive behavioural therapy in which -- using CFS as an example -- he described a cognitive-behavioural approach to somatisation, which he concluded was: *"the basis for a new evidence-based approach to psychosomatics"* (Psychosomatics 1997:38:356-362).

Sharpe maintained that: *"Patients present with symptoms, but physicians diagnose diseases. In many cases, however, no disease can be found….Such complaints are commonly referred to as somatization, somatoform, or functional symptoms….they lead to a considerable, but largely wasted, expenditure of medical resources on clinical investigations".*

Sharpe set out his concept of cognitive behavioural therapy, explaining that it was originally developed for the treatment of depression and that **it is based on a theoretical model of illness** which assumes that (1) illness is best understood using a broad perspective of biological, cognitive, emotional, behavioural and social components and (2) these components interact to perpetuate illness.

In Sharpe's model of "*illness components"*, it is important to note his interpretation of the biological component: *"Standard biomedical investigations are typically negative in CFS. This does not mean that the illness has no biological basis and* ***a number of physiological abnormalities have been identified. These include decreased physical fitness or 'deconditioning'*** *".*

There is no mention of organic pathology in Sharpe's model of the perpetuation of CFS, thus in his model, biological abnormalities extend only to loss of physical fitness and do not allow for pathogens such as viruses.

According to Sharpe, "*An important implication of this model is that psychological and social factors are regarded not only as consequences of the biological disturbance but also as causes of the disturbance*".

Sharpe's reasoning is thus circular: according to him, the effects of a cause can be the cause of the cause.

This statement by Sharpe may alert readers to the fact that normal standards of thought, science and logic appear to have been suspended in relation to their model of "CFS/ME" (which claims that biological, psychological and social factors all interact to perpetuate illness), because what is not explained is that these factors cannot suddenly start interacting only when people become sick --- they must be operating all the time in nature, so how can they be the cause as well as the consequence of illness behaviour?

Such a concept appears to be what has been described by a Professor of Neurology as "psychobabble" that lacks all scientific merit and should be totally rejected ("ME:PFS: Diagnostic and Clinical Guidelines for Doctors"; ME Association, 1991).

Of even more concern is that the Wessely School's beliefs about ME/CFS appear not to have advanced with the progression of medical science over the last twenty years.

Regarding CBT treatment for CFS, Sharpe concluded: *"**If the described model is valid, changes in relevant cognitions and behaviours should facilitate normalization of physiology and speed recovery**".*

Despite the fact that this was nothing more than an unproven and incomplete model, Sharpe stated: "*We need to increase the influence of the cognitive behavioural perspective, with the aim of achieving a paradigm shift in medical thinking and practice*".

Many people believe that the PACE Trial is a major step in promoting that paradigm shift and that the consequences for people with ME/CFS will be profoundly damaging.

Quotations from the Therapists' Manual on Cognitive Behaviour Therapy

This 162 page Manual *"draws a distinction between factors that precipitate and those that maintain"* "CFS/ME" and focuses on *"lifestyle, life events and personality"*. Therapists are taught that perpetuating factors include *"fear about activity making the illness worse"* and *"avoidance of activities"* but also – confusingly -- that *"over-vigorous activity"* perpetuates the illness, as well as *"symptom focussing"*, *"life stress and low mood"* and *"perfectionism"*.

On page 7 the authors (Mary Burgess and Trudie Chalder) state: "*Common to **these illnesses** are the symptoms of physical and mental fatigue, usually made worse by exertion. Other symptoms may include difficulty with memory and concentration muscular and joint pain, unrefreshing sleep, headache, tender lymph glands, and sore throats"*.

There are three points of note: (i) ME/CFS/PVFS is classified as one neurological disorder, not several (*"these illnesses"*), and the defining feature is post-exertional malaise with physiological exhaustion, so by their choice of words the authors are acknowledging that more than one disorder has been included in the PACE Trial; (ii) cardinal symptoms of ME are not mentioned and (iii) the authors state "*other symptoms may include…"*, but if the patient has only fatigue and no other symptoms, that patient does not have ME and should not be included in a trial that purports to be studying ME.

On page 12 the authors state: "*Participants are encouraged to see symptoms as temporary and reversible and not as signs of harm or evidence of fixed disease pathology"*. How can such advice be given when the authors have no evidence that symptoms are either temporary or reversible? For non-medical therapists to give such incorrect advice to participants who may actually have ME is potentially dangerous.

Also on page 12 the authors state: *"The aim of this treatment is to change the behavioural and cognitive factors, which are assumed to be partially responsible for perpetuating the participant's symptoms"*: if "*behavioural and cognitive factors*" are only *"partially"* responsible, then there must be something else causing the symptoms, such as a physical disease process, which contradicts the Investigators' assumption that there is no pathology involved, and which further illustrates the lack of intellectual rigour of their "CBT model".

On page 12, under "Theoretical Model", the authors state: "*This model acknowledges that the participant's beliefs and behaviours are influenced by available information and attitudes of families and friends and that these may also need to be addressed"*, which indicates that, no matter if those beliefs are correct, family and friends are to be similarly cajoled into changing their beliefs, even though family and friends have not signed consent forms agreeing to have their thinking restructured. This does seem to be akin to a cult that is determined to impose its own ideology as widely as possible.

On page 14 the authors state: "*It is their planned physical activity, and not their symptoms, that determines what they are asked to do"*, which once again appears to be indoctrinating participants to ignore what may be serious symptoms.

On page 15 the authors state: "*A mild and transient increase in symptoms is explained as a normal response to an increase in physical activity"*. Symptoms may not be mild and transient and may be an abnormal response caused by underlying pathology. How can therapists know that this is a *"normal response"* and not caused by underlying pathology?

This is an assumption, not a fact, and therefore participants and therapists should be made aware of this.

Post-exertional symptoms may be indicative of cardiac output being unable to meet increased metabolic demand which, if exceeded only momentarily, results in death.

On page 17, Burgess and Chalder make an astonishing assertion: "*There is no clear evidence of the virus persisting once CFS/ME has become established"*. Such an assertion is readily disproved by the literature that

was available even before the publication in "Science" on 8th October 2009 of the discovery of the retrovirus XMRV that in the USA has been shown to be strongly associated with ME/CFS (for example, Archard et al; Lerner et al; Chia et al – see Section 2 above).

On page 18, under "*What factors perpetuate CFS/ME?"*, the authors state: "*According to this model, the symptoms and disability of CFS/ME are perpetuated predominantly by unhelpful illness beliefs (fears) and coping behaviours (avoidance)*". This is another assumption portrayed as fact.

Also on page 18, the authors discuss "*Avoidance of activities*" by people with "CFS/ME", but the paragraph is self-contradictory; it says that people with "CFS/ME" avoid activities because of fear yet, despite this fear of activity, patients resume activities, and this resumption of activity causes them to avoid activities because of fear. By endeavouring to construct their own "vicious circle" model to underpin their own beliefs, the authors appear to reveal a singular lack of reasoning.

On page 19 the authors assert that people with "CFS/ME": "*will often pay a lot of attention to their symptoms which may result in an exacerbation of symptoms"*. -- another assumption presented as fact: there is no evidence that people with ME pay more attention to their symptoms than people with other serious organic diseases.

On page 21 the authors state: "*Treatment is focused on addressing the cognitive and behavioural factors that maintain the vicious circle of CFS/ME"*. This is a declarative sentence (ie. that "CFS/ME" is maintained by beliefs and behaviour): once again, this is a Wessely School assumption that is stated as fact.

On page 22 the authors assert: "*Treatment aims to help participants improve their level of functioning which in turn reduces fatigue"*. This clearly states that improving levels of functioning reduces fatigue: apart from being back-to-front (reducing fatigue is more likely to improve functioning), this is another Wessely School assumption stated as fact.

Also on page 22, the authors are explicit: "*A variety of cognitive and behavioural strategies will be discussed with participants during their CBT sessions to help them improve functioning as a primary goal"*. It is clear that the primary goal is *"to improve functioning"* (therefore reducing fatigue seems not to be the primary function). This is essentially the UNUMProvident *"back to work, with or without symptoms"* mantra (UNUM's "Chronic Fatigue Syndrome Management Plan" dated 4th April 1995 authored by Dr Carolyn L Jackson).

On page 23, the authors state that frequent unhelpful cognitions include the patients' fears that: "*activity will make my problems worse"*. As these "fears" may be based on patients' long experience of such exacerbations (documented in a wealth of ME/CFS literature as post-exertional malaise) they must be taken seriously. If the PACE Trial therapists are encouraged to disregard caution that might be vital to participants' health, this raises serious ethical questions.

Pages 28 and 29 of the CBT Manual for Therapists summarise the central assumptions made in the CBT arm of the PACE Trial by Mary Burgess and Trudie Chalder:

i) participants are assumed to have no pathology, because the authors state that CBT and GET do not work from a pathological assumption

ii) CBT and GET will work from a "*deconditioning hypothesis*" (that is, the authors assume that participants are fatigued because they are physically unfit); the authors do not consider that symptoms result from disease, but from using deconditioned muscles

iii) APT <u>does not aim</u> for an improvement in function

iv) CBT/GET encourage patients to ignore symptoms and therapists will not encourage "*participants to listen to their body*", rather, they will encourage them to "*consider increase symptoms* (sic) *as natural response to increased activity"*

v) CBT will "*explore unhelpful thoughts*" and "*fear avoidance, and anxiety related to CFS*".

The corollary is that the participant's fatigue and other symptoms are the result of deconditioning, anxiety, fear avoidance, unhelpful thoughts and **do not result from physical disease**, with the inescapable conclusion that ME/CFS is considered a psychological disorder. Indeed, the Manual teaches therapists how to manage participants who believe they have a physical disease and how to persuade them that this is not the case and to dissuade them from seeking further medical attention.

The "*CBT Model of CFS/ME*" as it is explained in the CBT Manual for Therapists adduces other factors, often risible and contradictory, as contributing to the "*maintenance*" of the participant's ME/CFS. These include:

- "*being too busy"* (p 17)
- "*being too inactive"* (p 17)
- *"fear of activity*" (p 47)
- *"working excessively hard"* (p 81)

- welfare dependency:

- *"being on benefits"* (p 51)
- *"being in receipt of benefits"* (p 92)
- *"if a participant is in receipt of benefits, or income protection (IP), this may inadvertently lead them not to push themselves too hard."* (p 97) *"Evidence from research trials has indicated that patients who are in receipt of benefits or permanent health insurance do less well than those who are not in receipt of them. In reality, benefits and IP can help patients financially in the short term, but prove to be an obstacle to getting better in the long term"* (p 99)

- adopting the sick role:

- "*sometimes relatives and friends do more than may be required, e.g. all of their shopping, cleaning, cooking, resulting in increased dependence of the person with CFS/ME"* (p 44)

- believing that ME/CFS is a physical disease:

- "*a purely physical attribution of illness may be a block to overcoming their CFS/ME"* (p 48)
- *"[belief in] an ongoing virus"* (p 63)

- work or relationship issues (p 34):

- "*attitudes of family and friends"* (p 12)
- *"inadequate housing"* (p 50)
- *"financial difficulties"* (p 50)
- *" meeting people socially"* (p 97)
- *" being responsible for the running of the home, their work, paying bills" (p 97)*
- *"lost their confidence in their ability to do a variety of things, e.g. travelling alone, meeting new people etc"* (p 97)
- and, perhaps most bafflingly, concerns about *"not being good enough"* (p 101).

ME/CFS is thus presented as a "condition" (not a disease) that can be caused both by doing too much and by doing too little; by working excessively hard but also by being dependent on welfare.

Physical factors, such as infection, are only considered to play a role in *triggering* the illness; the Wessely School model does not allow for physical factors to play any part in *perpetuating* the illness.

Any viral or bacterial infection that was present at the start of the illness is assumed to have fully resolved.

The symptoms and disability experienced by the participant are therefore "maintained" by what the participant believes and how the participant behaves, which seems remarkably like "blaming the patient".

It is notable that in numerous places throughout the CBT Manual for Therapists, reference is made to alleged personality traits of people with "CFS/ME", a prominent one being alleged "perfectionism": on page 54, *"perfectionism"* is listed as a trigger for the disorder; on page 101 the authors state: "*Any regular themes that occur should be discussed with a view to identifying unhelpful core beliefs. Themes may include not being good enough (related to perfectionism)"*; on page 124 (*"What causes CFS/ME")* the authors list *"Having high personal expectations and driving to do things 'perfectly' can cause…fatigue"* and on page 158, in *"Evaluation of Progress"* the authors suggest that factors which may have preceded the participant's "CFS/ME" are *"constantly being busy…aiming for perfection"*.

This does not accord with the published evidence of Professor Wessely himself. As noted by Twisk and Maes (Neuroendocrinol Lett 2009:30(3):284-299): "*Another misconception is the central role of specific personality traits presumed by the (bio)psychosocial model. Wood and Wessely, the captain of the (bio)psychosocial school, for example pointed out very clearly* (J Psychosom Res 1999:47: (4):385-397) ***that no differences between patients with ME/CFS and rheumatoid arthritis in measures of perfectionism,*** *attitudes toward mental illness, defensiveness, social desirability, or sensitivity to punishment (a concept related to neuroticism)* ***were found. The authors stated their study also invalidated the 'stereotype of CFS sufferers as perfectionists*** *with negative attitudes towards psychiatry' ".*

Seemingly, as Chief Investigator, Professor Peter White was content to permit Trudie Chalder and Mary Burgess to disregard the evidence of Professor Wessely (who is in charge of the PACE Clinical Trial Unit).

Establishing a shared multifactorial understanding

Therapy will commence by "*Establishing with the participant a shared multifactorial understanding of their illness that takes into account predisposing, precipitating and maintaining factors"* (p 22).

There are two important observations to be made at this point:

i) the therapists appear not to have been taught about the extensive biomedical evidence on ME/CFS but only about the Wessely School's psycho-behavioural model presented in the Manual, thereby denying them what could be vital information in determining the suitability of the therapy for an individual participant

ii) what if a "*shared multifactorial understanding of the illness"* cannot be established? The therapist has been taught to work within a very particular view of what ME/CFS is and therefore a shared understanding can only occur if the participant is willing to change his/her beliefs to match those of the therapist.

Given that participants have been informed on five separate occasions in their own CBT Manual that they can *"overcome their CFS/ME"* (ie. they can expect to be cured) by the application of CBT, it is possible, indeed likely, that some participants would feel pressurised into agreeing with their therapist: for instance, **any participant who thought s/he had a physical disease would have to change that belief, as such a belief is considered within the CBT model to be a barrier to recovery.**

The authors appear to have acknowledged that participants' unwillingness to accept this model of CFS/ME could be a significant problem so they address the issues of "*engagement*" and "*managing potential difficulties*" in great detail.

Engagement

Pages 31- 33 of the Manual cover the topics: "*Engagement, Warmth and Empathy, Sensitivity"* and *"Collaboration".*

"In order to engage the participant in therapy, it is important that the therapist conveys to the participant their belief in the reality of their symptoms, distress and handicap. The therapist should be able to demonstrate a sound knowledge of CFS/ME": regardless of how sound their knowledge, the therapists are only allowed to work within the very limited psycho-social model set out in their Manual.

" People with CFS/ME are often sensitive to the over-emphasis of psychological factors": in this CBT arm of the trial there is assumed to be no pathology, therefore the illness has to be considered by the therapist as "psychological", but the therapist must simultaneously conceal this from the participant in order to maintain their engagement, whilst nevertheless convincing participants that there is no physical disease process, so this feigned concern appears duplicitous.

" It is important that you show respect for their beliefs on the cause(s) of their illness": it must be questioned how it is possible for the therapist to show respect for someone's beliefs when the therapist is just about to engage in a systematic programme to change those beliefs.

The therapist is told to "*avoid challenging* (participants' beliefs) *as this is likely to provoke strong emotion and will reduce the likelihood of a good therapeutic relationship being established. In order to maintain participants' engagement throughout treatment, it will be important that you continue to use an integrative model and avoid promoting a rigidly dichotomous view of physical and psychological illness"*: the authors seem curiously unaware that the model presented in the Manual is a dichotomous model because it does not allow for the presence of physical disease.

Given the model that is set out in their Manual, it is difficult to see what biological factors therapists could possibly include in their integrative model and, equally, it is difficult to see how the participant can view this as anything other than a "psychological illness", as their only treatment is a therapy designed to change what they believe and what they do.

"*Warmth and Empathy*

"Empathy is something that we will hopefully tend to do with all patients without thinking about it. However, with this client group it is particularly important. Many of them will report at least one upsetting incident relating to a health professional, whether it is not being believed, not being taken seriously or being told it is all in their mind". Again, the authors demonstrate a curious lack of insight: the "CBT model" is an "all in their mind" model; if it is not, then why do they believe that the exclusive application of a psychological therapy can be curative?

"Some participants will feel guilty about being ill and blame themselves for their predicament": **it is sadly ironic that the section on "*empathy*" which recognises that some "*participants will feel guilty about being ill and blame themselves for their predicament*" continues to demonstrate the authors' failure to comprehend that the "CBT model of CFS/ME" does exactly this: the participants are assumed to remain unwell because of what they believe and how they behave.**

"It is therefore very important that you convey warmth and empathy at your first meeting. Throughout your treatment sessions, it will be important that you continue to show warmth and empathise with your participant": this instructs the therapist to win the patients' trust from the start, a vital component of a process that encourages

someone to change their fundamental beliefs about the such an important issue as the nature and causation of their disease.

"There is no doubt that getting people to change previous routines can be difficult in a number of ways. The participant may be very fearful of changing the way they do things, fearing worsening of the symptoms. They may find that their symptoms initially worsen when starting their CBT programme": if participants' symptoms do not worsen with exertion, then they do not have ME and should not be in an MRC Trial that purports to be studying those with ME.

That symptoms do indeed worsen in ME/CFS patients after exertion has been established and has been shown in Section 2 above. Moreover, Peter White's own study showed that the pro-inflammatory cytokine TNFα remains elevated three days after exercise in "CFS/ME" patients (JCFS 2004:12(2):51-66).

"Acknowledging the challenges associated with the programme is important if you are to win their trust": how is it possible to win "trust" when the therapist does not disclose to the participant the central assumption of the CBT model that there is no physical disease process and that symptoms result from psychological and social factors?

Throughout the Manual, the therapist is reminded on at least eight separate occasions to demonstrate empathy and warmth.

"Collaboration

"Collaboration is an essential skill in working with people with CFS/ME. Up to the point of meeting you, many participants will not have been included in the management of their illness. Collaborating throughout treatment will help participants to feel more involved in their treatment and will help them to regain some sense of control": this again demonstrates the authors' lack of insight: how can patients regain some sense of control when they are being manipulated into changing their correct beliefs and behaviour and it is therapist who is "taking control"?

"You will be demonstrating a collaborative style at your first meeting when you individualise the CBT model to their illness. By this we mean drawing a model together, examining factors they think have been responsible for triggering as well as maintaining the illness": patients may correctly think that maintaining factors are a virus and a dysfunctional immune system, so it is highly likely that a significant proportion of participants with ME/CFS will – if not screened out by use of the Oxford entry criteria -- report that they have a physical disease caused by a viral infection and this particular belief is one the therapist must address, as belief in "*an ongoing virus*" is considered a barrier to recovery.

"Agreeing an agenda for each treatment session, asking for their input in making suggestions for their activity programme and evaluating previous sessions will help participants to feel valued and included in the treatment process": the "*collaborative*" model proposed, one that promises to help the participant "*regain some sense of control*", may actually achieve the opposite by subtly dis-empowering them.

What purpose is served by asking the participant for their opinion about what is wrong with them if, eventually, they must accede to the therapist's understanding of ME/CFS?

Page 35 of the Manual offers further advice on maximising engagement:

"Do's: …….

- *"…..Show empathy, warmth, sensitivity and understanding during the assessment process (and thereafter)"*

- *"….Tell the participant that you will look forward to working with them over the coming months"* (more false empathy, because the therapist must first engender "trust")

"Don'ts …..

- *"…Challenge the participant about their illness attributions"* (ie. the therapist must not tell the patient the truth about their own beliefs, namely that "CFS/ME" is a mental disorder).

Page 39 of the Manual instructs therapists to ask participants about occupation, benefits, and any income protection (IP) policies they may have; whilst it is understandable to seek demographic information and to enquire about occupation, asking specifically if a participant is on benefits and if they have IP is highly unusual and appears to reveal the motives behind the PACE Trial.

Page 43 of the Manual directs therapists to ask specifically if a participant belongs to an ME organisation, which again seems to reveal the PIs' motives, since the Wessely School believe that membership of such an organisation militates against recovery.

Page 45 of the Manual (and throughout) focuses on "fatigue". There is no mention of cardinal ME symptoms, as these do not feature in the Wessely School model. Instead, therapists must establish if there is "*phobic anxiety"*, or if the patient feels *"tense"*, or if there are any situations in which the patient feels *"uncomfortable, e.g. in supermarkets*", or if the patient has suffered from *"panic attacks".*

Managing Participants who believe they are physically ill:

It seems that the PIs recognised that there could be significant problems maintaining the engagement of participants who believed they had a physical disease and therefore the therapists were provided with specific instructions on how best to manage them.

Page 47 of the Manual provides the Wessely School's beliefs about this issue in a section entitled: "*Beliefs about the cause of the illness and why it is persisting*":

"*Exploring the participants' beliefs about their illness is essential before you discuss the CBT model for CFS/ME. It is vital that you incorporate their own beliefs into the CBT model that you discuss with them so that they feel that their opinions matter and have been taken seriously"*: how is it possible for a therapist to incorporate a participant's beliefs into the "CBT model" if the participant's beliefs are at variance with the assumptions of the model?

It would appear that therapists are being instructed to solicit the beliefs of participants *"so that they feel their opinions matter and have been taken seriously"*, but it seems that participants' opinions do not matter and are not taken seriously because the therapist is instructed to change them. **It is reasonable to question how seriously the beliefs of a participant are taken when the purpose of therapy is to change any beliefs that the therapist has been taught are a barrier to recovery.**

"*Participants will have been diagnosed with CFS/ME, but it is important to ask them what they feel has caused their problems and what they feel is keeping their illness going"*: if a participant does not think that their problems are caused by ME (or by "CFS/ME"), then what are they doing in the PACE Trial?

"It is useful to gain an impression of their strength of belief in the cause, particularly if they feel that it is caused by something physical, e. g. a virus. ***If a participant is convinced that their CFS/ME is caused purely by something physical, e.g. an ongoing virus, you will need to carefully address their beliefs during the course of CBT to broaden rather than directly challenge causal attributions****"*: these ambiguous instructions seem aimed at displacing the participant's rational belief that a virus may be causing their symptoms, yet the authors of the Manual have no evidence that a virus is not implicated and ignore the evidence that viruses are implicated.

"A purely physical attribution of illness may be a block to overcoming their CFS/ME": this is a clear statement that the authors maintain that participants who believe they are physically ill must be persuaded that this is not the case, and they must change what they believe and how they behave if they want to recover.

Although therapists have already been instructed to enquire about benefits and income protection, page 51 of the Manual directs the therapist to revisit this issue: "*Although you will have asked about employment and benefits, it would be useful to find out, if they are not working, whether they want to return to their previous job. There is some evidence to suggest that that being on benefits and/or income protection (IP) are poor prognostic factors as they are contingent upon the patient remaining unwell"*: the use of the term "income protection" is significant – who outside the insurance industry uses the term "IP" and why is it featuring in a clinical trial?

Participants were to be questioned in detail about their financial situation (for example: *"What are your current wages / salary before tax? Please indicate if this is weekly / monthly / annually. If participants choose not to give an answer, please use the prompt card to show income brackets and record the letter that corresponds to the participants' income. [Code / weekly sum: up to £100 / A1; £101-250 / BB; £251-500 / AC etc]"* with similar alphabetical codes for monthly and annual brackets. Participants were also to be closely questioned about which benefits they receive, and especially about the amount of income protection they might be receiving, for example: "*In the past six months, have you received any one-off payments for income protection or insurance schemes?"* and "*Are there any benefits that you don't receive but which are currently under negotiation or in dispute?"*. Participants were not told why these questions were being asked, namely, that the PIs believe that being in receipt of such benefits is a barrier to recovery because being *"…in dispute/negotiation of benefits or pension"* predicts a poor response to therapy (Full Protocol page 55). Were participants fully informed of the special interest of the DWP in the trial and that the PACE Trial is the only clinical trial that the DWP has ever funded?

As the PACE Protocol in which these inquisitions are stipulated was approved by the West Midlands MREC, it is clear that the MREC saw no ethical problems in such financial prying as a component of what purports to be an MRC clinical trial. How many other MRC clinical trials subject participants to such financial inquisition?

Pages 63-65 of the Manual offer further advice on managing participants who have a "*Fixed physical attribution of illness*" (ie. who believe they have a physical disease).

"Fixed physical attribution of illness

"Participants who hold a fixed physical attribution of their illness are likely to have difficulties engaging with a therapy that they feel is going to be looking at their "behaviour' and "thought" patterns. Holding a purely physical attribution appears to be occurring less than it used to do in clinical practice (this is disputed by many people), *but it still occurs. Examples of a physical attribution may include an ongoing virus, permanent damage being caused from an allergic response, an unalterable disease, etc".*

"If participants are insistent that there is an ongoing "physical" problem, it is rarely helpful to directly challenge them on this point": how can the therapist know that there is not an ongoing physical problem?

Is it ethical for someone who is not medically qualified (and professionally negligent if they are) to treat someone as though they had no physical disease without clearly informing them of that assumption?

"It is important that you acknowledge that their illness is real but its effects can be reversed by the way they manage it"*:* there are two issues here; (i) to instruct the therapist to describe it as "real" (which most people will interpret as an organic disorder) when the model dictates otherwise, could mislead participants and (ii) the PIs do not know that its effects can be reversed – that is the hypothesis that is being tested the trial.

"The way that you present the rationale for treatment will be particularly important otherwise they may feel that you are trying to "psychologise" the illness": this is could be interpreted as instructing the therapists to be dishonest, because the CBT model is self-evidently a psycho-behavioural model.

" It is particularly helpful if they are sceptical about this approach, to draw a model of illness together, to look at all the factors that may have triggered it and be involved in maintaining it. Patients often feel reassured when they are informed that CBT helps people with a wide range of health problems including cancer, chronic pain and diabetes. It can be helpful for this group of patients to try to view aspects of CBT as an experiment".

Therapists are provided with an illustrative dialogue, which seems structured to ensure that questions are phrased so that the participant has to agree with the therapist and is gradually coerced into accepting the rationale for continuing with CBT:

"The following dialogue may help to engage participants in therapy.

"Therapist: Up to now, you have been trying to manage your illness by doing things when you feel relatively ok, i.e. when your symptoms are not too bad. However; from what you have said it seems that you can tend to push yourself too much when you have a bit of energy, resulting in you feeling exhausted and resting until your symptoms have reduced a bit. Does that sound right?

"Participant: Yes.

"Therapist: What I am proposing, is that I try to help you to do things in a slightly different way, i.e. that you establish a routine of doing activities and taking breaks/resting at regular times. This will help your body clock to become used to doing things at set times again. How do you think that would make you feel?

"Participant: Worried. What if I don't feel like doing things at certain times. What if I feel really awful when I am supposed to be doing something, surely pushing myself will make me worse?

"Therapist: I understand that what I am proposing may seem a bit worrying to you. However how would you feel about starting with very small goals? I would suggest in the first instance is that we look at all of the activity and rest that you are having in an average week. I am going to ask you to fill in an activity diary and sleep diary for the next week and to bring them with you to your next appointment. So for the next week you will not be doing anything different, except filling in your diaries, would that be ok?

"Participant: Yes, that's reasonable".

Pages 67-69 discuss how to manage participants who request further medical tests believing a physical cause for their illness has been missed. Despite the minimal investigations the participants received, the authors assume that this offers definitive proof that there is no underlying pathology and that nothing has been missed; consequently, therapists are provided with highly specific instructions on how they are to dissuade participants who believe that they are physically ill from seeking medical care.

"Feeling that a physical cause has been missed and wanting further investigations:

"Some participants may not hold a specific belief about what is wrong with them, but feel that despite many investigations, something has been missed".

"Participant: I am feeling so exhausted, I really cannot believe that all my tests are clear. I feel sure that something has been missed. I think I might go to my GP just one more time to ask him if there are any other tests that I could have.

"Therapist: I can understand that with feeling the way you do, you feel something has been missed. However what I am proposing to do is to help you to understand why you feel as bad as you do and also to see if we can help you to feel a bit better in the process. Would that be o.k. ?

"Participant: But what if something has been missed that could be easily rectified?

"Therapist: From your notes I can see that you have had many tests, none of which point to a simple explanation for your fatigue. It therefore seems unlikely that someone would be able to detect an obvious cause": contrary to what the therapist is instructed to say, patients with ME/CFS have usually had very few medical investigations, not least because the Wessely School's recommendation in the 1996 Joint Royal Colleges' Report (CR54) specifically stated: "*no investigations should be performed to confirm the diagnosis"* (page 45).

"Therapist: Although I can see the temptation of seeking further clarification of your problems, in reality what can happen is that you end up feeling more confused. I believe that your fatigue is a symptom of a bigger picture and I would like to spend some time discussing my thoughts on this matter with you. I wonder how you would feel about that?

"Participant: Well, I suppose it wouldn't do any harm" (it could in fact do a lot of harm to ignore some symptoms).

"Therapist: What I suggest that we do is to get a large piece of paper and write down what we do know about your illness, including your symptoms, what was happening at the time you became ill and ways that you have been managing to deal with your illness to date. This information may help us to look at factors that may have triggered it and factors that may be involved in keeping it going. I hope this will help us to make some sense of your illness together before we move on to discussing ways of overcoming it. Would you give my suggestion a go?"

"Participant: Yes".

In pages 80 to 162 of the Manual the authors then consider the 14 sessions of CBT that are to be delivered to participants. Much of the material is reiterated, particularly the "*vital"* need for *"genuine interest, warmth and empathy"*. This seems dishonest because the empathy is not genuine: it appears contrived in order to ensure compliance.

Session 1 focuses on an explanation of the "*cognitive behavioural model*" of "CFS/ME" and the "*vicious circle"* of "*unhelpful illness beliefs"*, together with emphasis on "involving" the participant. There is no mention of on-going physical disease. The therapist is again provided with a dialogue: "*From the diagram we've drawn together, it seems that several factors are involved in keeping your CFS/ME going"*: how does the therapist know this? It is pure speculation that any of the factors in the "CBT model" maintain ME/CFS.

In Session 2 the therapist introduces the concept that participants are ill because they have dysfunctional beliefs and behaviour, the object of therapy being to persuade them to change those beliefs (ie. to coerce them into accepting that psychological factors, not physical factors, are important). The patients must agree to change their beliefs in order to recover, so where is the "essential" element of "collaboration"?

In Session 4 the therapist is instructed to "*elicit cognitions that may interfere with homework"* and participants are to start an "*unhelpful thoughts diary"*. An example of "unhelpful thoughts" is given: *"I may hurt more to start with".*

This brings to mind Trudie Chalder's approach referred to above:

*" **'We expect*** (name) ***to protest, as well as the activity causing him a lot of pain. This may result in screams….it may feel punitive'** "* (see Section 1 above).

Sessions 5 – 7 are based on *"cognitive work"* in which the participant's *"thoughts, feelings and behaviour…illness attributions (and) self esteem*" will be discussed. "*Participants will be taught how to identify thinking errors"* -- this assumes that participants do have "*thinking errors*" -- and therapists are to tell participants that "*A common problem is a difficulty in identifying unhelpful thoughts"*. Consequently, the participant, who may not have thinking errors, is instructed to re-interpret in a negative (ie. "unhelpful") light thoughts that may not be unhelpful.

In Sessions 8 – 11 therapists are to "*discuss potential blocks to recovery"*, one of which is a participant *"being in receipt of benefits or income protection (IP)*".

"Evidence from research trials has indicated that patients who are in receipt of benefits or permanent health insurance do less well than those who are not in receipt of them. In reality, benefits and IP can help patients financially in the short term but prove an obstacle to getting better in the long term": that patients who are in receipt of financial support may be more seriously ill -- and therefore do less well -- than those who are not in receipt of it is not considered.

Income protection is once again addressed, at considerable length, and in a way that seems highly unusual in a clinical trial. Therapists are directed that: *"it is helpful for you to offer to write to employers, insurance companies, be involved with their occupational health department or whatever is necessary to help the participant to meet work-related goals".*

Is it the job of a non-medical "therapist" in a clinical trial to encourage a participant -- who may be seriously ill -- back to work?

Other blocks to recovery are said to be a fear of social situations, being responsible for running the home, work, paying bills etc.

Also in these sessions, "*the content of their thought diaries should be reviewed*"; "*suggestions to increase their awareness of thinking errors should be discussed*"; and "*The role of unhelpful thoughts in recovery should be discussed".*

In Sessions 12 – 14 (*"Preparing for the future"*) participants are to be informed that: "*the follow-up period is when many clients make the majority of their improvement and that the end of treatment should therefore not be seen as the end of recovery".*

Clearly, then, it is only after 14 sessions of CBT have finished that most people are said to make the majority of their improvement.

This does not accord with what Peter White – to whom acknowledgement is made by Mary Burgess and Trudie Chalder – said in the St Bartholomew's submission to the NICE Guideline Development Group: "*If a therapy is not helping within a few months, either the therapy or the diagnosis or both should be reviewed and changes considered".*

Perhaps this is just one more illustration of the many ambiguities and contradictions that pervade the PACE Trial Manuals.

This CBT Manual for Therapists provides evidence of a central flaw in the MRC PACE Trial: on page 7 Burgess and Chalder state: ***"No specific cause for CFS/ME has been identified"*** (ie. the Investigators concede that they do not know what causes "CFS/ME"), but on page 28 the authors state that CBT does not work from a pathological assumption (ie. although the cause of "CFS/ME" is unknown, participants are assumed to have no physical disease).

On page 12 the authors state: "***Participants are encouraged to see symptoms as temporary and reversible and not as signs of harm or evidence of fixed disease pathology***".

Here, then, is the evidence that participants are not told that the above assumption has been made by the Principal Investigators, and that participants are to be persuaded that what the PIs acknowledge to be an unproven assumption is actually established medical fact, when such is not the case.

Is this ethically acceptable within a UK clinical trial?

Quotations from the Participants' Manual on CBT

This 127 page Manual for Participants on the CBT arm of the PACE Trial is disturbing.

Once again, the authors have been careless over terminology: on pages 4 and 5 of this Manual the disorder is incorrectly referred to as *"Myalgic Encephalitis"* instead of Myalgic Encephalomyelitis.

Differences between the Therapists' and the Participants' Manuals on CBT are striking.

For example, in the participants' Manual, one particular sub-heading states: "***Factors that may contribute to the development of CFS/ME",*** whereas in the Therapists' CBT Manual the same sub-section is entitled ***"What factors contribute to the development of CFS/ME"*** (ie. no use of the word "*may*", with the information given as fact). The same applies to the sections on ***"Factors that may maintain CFS/ME"***.

All the reasons given as "maintaining factors" are the assumptions and prejudices of the Investigators but are presented to participants as facts. Participants are told that maintaining factors include resting too much (assumption stated as fact); over-vigorous exercise alternating with resting for long periods (assumption stated as fact); receiving confusing messages about the illness (assumption stated as fact); an irregular bedtime (assumption stated as fact – the authors of this Manual are assuming that irregular sleep maintains ME/CFS rather than it being an effect of the disease); symptom focusing (assumption stated as fact – there is no evidence that participants are prone to "symptom focusing" -- it is pure speculation to assert that this maintains the illness); worries about activity making the illness worse (activity may well make the illness worse), and life stress / low mood (there is no evidence that low mood maintains ME/CFS).

In a significant departure from acceptable standards in a clinical trial, this Manual assures participants and their families that CBT is *"a powerful and safe treatment"* and, as long as participants follow the programme described in the Manual, they can expect to *"overcome their CFS/ME"* (ie. they can be cured).

This is the hypothesis that is being tested in the trial, yet it is stated as fact in the participants' Manual. This seems to be a deliberate invocation of the placebo response, which is unethical in a clinical trial.

Randomised controlled trials (RCTs) are considered the gold standard in medical research because researchers understand the confounding influence of a placebo response. It is hard to overstate the significance of the PACE Trial Investigators' methodological error: **as a consequence of encouraging a "positive expectancy" in two arms of the trial (CBT and GET) but not in another arm (APT), the data produced by the PACE Trial, and any conclusions based on that data, are likely to be scientifically worthless.**

To mislead patients by promising a cure when there is no such certainty is in breach of the General Medical Council (GMC) Regulations as set out in "Good Medical Practice" (2006):

"*Providing and publishing information about your services – paragraphs 60-62*

60. *If you publish information about your medical services, you must make sure the information is factual and verifiable.*

61. *You must not make unjustifiable claims about the quality or outcomes of your services in any information you provide to patients.* ***It must not offer guarantees of cures****, nor exploit patients' vulnerability or lack of medical knowledge".*

In this Manual, however, authors Mary Burgess and Trudie Chalder, neither of whom is medically qualified (which places them outwith the jurisdiction of the GMC), make such claims repeatedly, as do Professors White and Sharpe (see below)**.**

However, as Chief Investigator, Professor Peter White must bear overall responsibility for the content of the Manuals, and both he and Professor Michael Sharpe as another Principal Investigator are subject to the GMC regulations, which seem to have been disregarded in this instance, because the clinician's duty of care not to offer guarantees of cures seems not been followed, for example:

Page 4:

"***This manual aims to provide you with useful information and strategies to help you to overcome your chronic fatigue syndrome (CFS)/ myalgic encephalitis / encephalopathy (ME).***"

"***Many of the strategies described in the manual are based on cognitive behaviour therapy, which has been shown to be effective in treating a wide range of problems, including CFS/ME.***"

"***The information has been set out in an order that is commonly used by people to overcome their CFS/ME.***"

Page 17:

"***CBT is designed to help you to discover the most useful ways of managing and overcoming your illness.***"

Page 35

"Setting targets is a very important step in helping you to overcoming your CFS/ME".

Page 114:

"***Hopefully this manual and your sessions of cognitive behaviour therapy will have helped you to find some useful ways of managing your CFS/ME and you will be well on your way to recovery.***"

Page 123:

"***Cognitive behaviour therapy (CBT) is a powerful and safe treatment which has been shown to be effective in a variety of illnesses, including CFS/ME, headaches and back pain.***"

"***Many people have successfully overcome CFS/ME using cognitive behaviour therapy, and have maintained and consolidated their improvement once treatment has ended.***"

Page 126:

"***As long as a good balance of activity and rest is maintained, then recovery will be sustained.***"

Page 126 of the Participants' CBT Manual states: "*Information for Relatives, Partners and Friends*: *setbacks can occur at any time. They are a 'blip' in the recovery phase and certainly do not mean that CBT has failed".*

Such an assertion appears to be misleading, since what the authors of the Manual casually dismiss as a 'blip' may in fact be a major relapse that might last for weeks, months or years and might even be life-long.

This Manual is constructed in such a way as to give the impression to participants that the PACE Trial staff accept that "CFS/ME" is a physical condition by their expedient use of the word "physiological" ("*Physiological Aspects of CFS/ME"*-- pages 9-17), which disguises the fact that the therapists have been taught that participants are deconditioned (deconditioning being a *"physiological"* condition), whilst making no mention of pathophysiology, a tactic that seems misleading.

Given the length of this section in the CBT Participants' Manual, it is noteworthy that the therapists' CBT Manual does not contain any similar "physiological" information but explains "CFS/ME" simply as the consequences of "*deconditioning"* and *"fear avoidance and anxiety related to CFS"*. Indeed, page 18 of the Therapists' CBT Manual appears to contradict this entire section in the participants' CBT Manual: "*Although it is acknowledged that lack of physical fitness may play a part in exercise-induced symptom production, physical fitness is not central to this conceptualisation of the syndrome"*.

The "*Physiological Aspects of CFS/ME"* section begins with the following paragraph:

"*Many people with CFS/ME are concerned that their distressing symptoms may be related to a disease that hasn't been detected. Others are concerned that a virus (if one occurred at onset) is still present or has caused physical damage to the body"* (ethically, the therapists should tell the participants that they do not believe any physical disease is present, thus enabling participants to make an informed choice about whether or not to disregard their symptoms or withdraw from the PACE Trial).

" Intensive research has tried to establish whether disease, deficiencies or any other abnormal changes in the body may explain the very distressing and debilitating symptoms experienced by people with CFS/ME. To date, it appears that there is no one cause of CFS/ME" (by this wording, the authors impart their own interpretation of the research and imply that there is no disease present; they fail to tell participants that they, as "experts", have already concluded that there is no "physical" cause).

This section continues:

"*Over time, reduced or irregular activity and increased periods of rest causes* (sic) *physical changes in the body. These changes cause unpleasant sensations and symptoms that can be very distressing. **It is important to point out that these changes are reversible with physical rehabilitation and/or exercise**"* (there is no evidence that the physical changes which occur in ME/CFS are reversible with rehabilitation and/or exercise; these are Wessely School assumptions stated as fact and it seems dishonest to misinform participants in this way).

"Research has looked at the effects of rest in healthy people when they reduce their activities and many similarities between people with CFS/ME and healthy inactive people have been noted" (how can *"the effects of rest"* cause swollen lymph glands, nystagmus, hair loss or mouth ulcers?).

It seems that Mary Burgess and Trudie Chalder are doing their utmost to explain the "physical" problems which they assume the participants will have read about as a consequence of deconditioning.

The authors then make assertions describing the effects of prolonged periods of inactivity on the body; according to them, these include:

"Changes in muscle function

- *"A decrease in the number of active cell mitochondria (tiny parts of the cell that act as a powerhouse)…the reduction of cell mitochondria has also been found in healthy inactive people. These changes may account for the feeling of a lack of power or energy in the muscles"* (Burgess and Chalder imply that this is true for participants, but they cannot <u>know</u> this because they have not performed muscle biopsies or carried out mitochondrial testing on the participants)

- *"As reduced activity leads to less efficient muscles, it is more difficult for the muscles to squeeze the blood back to the heart causing blood to pool in the lower part of the legs"* (whilst pooling of blood in the lower limbs has been shown to occur in many ME/CFS patients, there is no evidence that it is the result of inactivity)

- *"In all individuals, muscle pain and stiffness are a natural consequenc of beginning a new exercise programme or when unaccustomed exercise is taken"* (but in people with ME/CFS, it is the result of disease, not disuse, a proven and published finding which Burgess and Chalder ignore).

Burgess and Chalder assert that visual and hearing changes experienced by ME/CFS patients occur because *"prolonged bed-rest results in a 'headward' shift of bodily fluids".* This is a bizarre assertion; their speculation seems to imply that these symptoms are the patient's own fault for lying in bed too long, but as noted above, the same symptoms occur in ambulant ME/CFS patients, which means that, logically, their explanation cannot be correct.

The authors claim (on page 10) that postural hypotension is caused by *"cardiovascular deconditioning"* (but no tilt-table testing has been performed on participants as part of the PACE Trial) and that breathlessness results from inactivity (page 10) and from *"the physical effects of anxiety"* (page 14).

Participants are informed that *"sensitivity to light or noise"* and *"blurring of vision"* are caused by hyperventilation (page 15).

Burgess and Chalder state with assurance that "*(post exertional) pain and discomfort*" result from *"uneven stresses"* in *"unfit muscles"* (there is no mention of mitochondrial dysfunction).

The authors inform participants that: *"the low cortisol levels found in people with CFS/ME are probably caused by disrupted sleep and irregular activity"* (a seriously misleading sentence that reveals the authors' lack of biomedical knowledge; moreover, measurement of cortisol levels has not been performed on participants as part of the PACE Trial so Burgess and Chalder have no idea whether or not participants have low cortisol levels).

Participants are told that feeling *"hot"* is caused by inactivity, and that feeling *"cold"* is caused by inactivity.

They are also told that *"excessive and inappropriate sweating"* is caused by inactivity, as is *"difficulty in finding the right word"*; a *"sore throat"* is caused by hyperventilation, as are *"swallowing difficulties"* and *"muscle aches"*. They are also told that *"pain"* is caused by anxiety.

Participants are told that when the sleep patterns of healthy volunteers were deliberately disrupted "*to be similar to those with CFS/ME"*, the healthy volunteers developed symptoms *"similar to those of CFS/ME"* (a study of healthy volunteers tells us nothing about people with ME/CFS). Burgess and Chalder then say: "*However, when they were allowed to sleep undisturbed, their symptoms subsided"*, upon the basis of which Burgess and Chalder assert: "*This study indicates that a disturbed sleep pattern can cause some symptoms of CFS/ME but that these symptoms are reversible"* (the study does not indicate this: having said that healthy volunteers experienced symptoms that were *"similar to those with CFS/ME"*, it is unsustainable for Burgess and Chalder then to claim that the study showed that a disturbed sleep pattern can <u>cause</u> symptoms of CFS/ME – it is just as likely that disturbed sleep is the <u>result</u> of having the disease, nor does it indicate that these symptoms are reversible; the study only tells us that this is true for <u>healthy volunteers</u>).

The section on "*Autonomic Arousal in CFS/ME*" begins with the following explanation:

"*Autonomic arousal is an automatic physical response of the body to a threatening or stressful situation. ... When we are in a situation that makes us feel anxious, there is increased activity of the central nervous system and an increased amount of the hormone adrenaline is released into the bloodstream. These natural changes have a protective function in preparing us for action when we feel threatened or encounter a stressful situation. However, the physical feelings that we experience when anxious can be very unpleasant".*

The next paragraph begins: "*Having CFS/ME can at times be very stressful. Not only may you be dealing with your illness, but you may also have concerns related to your illness such as concerns about your finances, if you are unable*

to work..." and concludes "*These worries may at times trigger feelings of anxiety*", thus guiding the participant, step by step, from the "physical" sounding *"autonomic arousal"* to the conclusion that they may experience "*anxiety."*

The description of anxiety begins: *"The physical effects of anxiety…" (*thus transferring the focus back to "physical" language) and concludes (p 16) "*Everyone experiences the physical symptoms of anxiety in a different way...An increase in nerve activity and adrenaline production can precipitate feelings of exhaustion....During periods of prolonged physical exertion....there is increased activity of the nervous systems and increased adrenaline production...Limiting activity can perpetuate the physical effects of anxiety and lead to a further reduction of fitness and muscle strength."*

The sections on *"Physiological Aspects of CFS/ME"* and "*Autonomic Arousal in CFS/ME"* seem intended to provide participants with a "physiological" (ie. "physical") explanation for the cause of their symptoms and are presented as fact. The possibility that the symptoms may have a serious underlying pathoaetiology is never mentioned.

To reduce the complex multi-system organic disease ME/CFS to little more than phobic avoidance of activity is profoundly insulting to sufferers.

In summary, CBT participants are told by Burgess and Chalder that "CFS/ME" is (i) the result of reduced or irregular activity; (ii) loss of fitness; (iii) the "physical" effects of anxiety, and they are told that it is reversible with CBT, all of which are gravely misleading statements that do not apply to people with ME/CFS.

There is the usual emphasis on the Wessely School's assumption that there are differences between *"factors that precipitate and those that maintain it"* and on their model of *"a vicious circle of fatigue"* and participants are patronised as if in a kindergarten: "*In order to help you understand your CFS/ME better, you may like to draw your own vicious circle".*

Participants are given the Wessely School's explanation of the "CBT Model of CFS/ME"; they must set targets (eg. go for two ten minute walks daily); increase activity; learn to challenge and overcome unhelpful thoughts and beliefs; overcome "*blocks"* that make it difficult to progress (such as being in receipt of incapacity benefit or income protection); ignore symptoms and not succumb to them ("*set-backs can be irritating"*); keep activity diaries and, above all, they must break the "*vicious circle"* of "*fatigue".* No mention is made of the cardinal symptomatology of ME/CFS; all the emphasis is on "fatigue".

The usual inconsistencies reappear: participants are told how to plan activities for *"people who generally do too much"* ("CFS/ME" is said to be caused by deconditioning but the authors do not explain how people who usually do too much are also deconditioned); Burgess and Chalder are clearly not talking about people with ME/CFS but about people with chronic "fatigue".

As in the Therapists' CBT Manual, assumptions are stated as fact and are regularly repeated as though the authors know they <u>have</u> to keep reiterating them to convince participants that they are true.

The authors seem to be exploiting what Chalder herself knows to be the non-specific factors that underpin cognitive behavioural therapy, such as support, therapist time and attention, and "expectation" by using components traditionally associated with CBT such as collaboration, active participation, agenda setting, session format, use of Manuals, and homework, which Chalder knows cannot be reliably measured because *"self-reports are amenable to response bias and social desirability effects"* (K van Kessel, R Moss-Morris, T Chalder et al. Psychosomatic Medicine 2008:70:205-213).

Participants are expressly told that: *"the way you think about the situation will determine how you feel"* (page 40). This declarative statement (***"will determine"***) is grossly misleading. Neurobiological evidence is <u>not</u>

consistent with the assumption that cognitions are necessary for emotions (A Critical Look at the Assumptions of Cognitive Therapy. Glenn Shean. Psychiatry 2001:64:2:158) and physical reality cannot be changed by changing one's beliefs.

On page 56 of the participants' CBT Manual, the authors divide the "therapy" into two sections: section 1 is titled "*Tackling unhelpful thoughts"* (this section subtly invites participants to believe that they must have "unhelpful thoughts" even if they have no such unhelpful thoughts) and section 2 "*addresses the topic of tackling unhelpful assumptions and core beliefs"*.

The section "*Unhelpful thoughts associated with CFS"* (the authors forgot to add "ME" to their "CFS") addresses putative "unhelpful thoughts", for example:

"*Fears about their illness"* (assumption stated as fact) and the authors notably state: *"there are differing attitudes from "experts", relatives and friends not only about the illness itself, but also what you should and shouldn't do"* (by putting *"experts"* in inverted commas, Burgess and Chalder seem to imply that people who disagree with them cannot be considered experts about ME/CFS; furthermore, the authors are encouraging participants to disregard the views of family and friends if those views deviate from Burgess and Chalder's own views expressed in the Manual, which could easily engender discord within the family and result in unacceptable stress for the participant).

"Example of how an unhelpful thought related to fears about illness may affect other areas of a person's life:

"Situation: Woke up feeling exhausted. Thought: I must be getting worse" (participants might well be getting worse, but how would they know this if they are being systematically taught to ignore symptoms that may be a warning of potential harm?)

"Behaviour: rest for most of the day"

"Emotions: 'worried' about making CFS/ME worse"

"Physical: more aware of symptoms e.g. fatigue and aching" (again, Burgess and Chalder are pathologising normal human reactions – it is <u>adaptive</u>, not <u>maladaptive</u>, to pay attention when a particular activity causes pain; evolution has provided the human body with a system of communicating when something is wrong: the language of this system is called <u>symptoms</u>, and "hurt" <u>may</u> equal "harm").

Burgess and Chalder then set out their own beliefs about "perpetuating factors", in which they include "*having extremely high personal standards and self-expectations"* (there is no evidence that this is more true of people with ME/CFS than the population as a whole); *"worry about starting new things"* and "*doubting your own judgement"* (there is no evidence that these occur in ME/CFS patients).

Another "unhelpful thought" is said by Burgess and Chalder to be *"feeling frustrated about doing so much less than you used to be able to do"* (there is no proof that this is any different in patients with other chronic diseases such as multiple sclerosis; people with MS are not subjected to cognitive restructuring that is intended to convince them they that do not have an organic illness).

Participants are asked: "*Can you think of any personal examples of how 'perfectionist' thoughts have influenced other aspects of your life since you developed CFS/ME?"* (this seems to be a fishing expedition by Burgess and Chalder, and the participant may feel pressurised to invent "perfectionist thoughts" to please the therapist).

On page 60, the Manual provides "*characteristics of unhelpful thoughts"* and the authors state that one characteristic is that they are "*automatic: as with all thoughts, unhelpful ones tend to pop into our head rapidly and unexpectedly"* (how is "*automatic"* a characteristic of an "unhelpful" thought if it is true of <u>all</u> thoughts?); participants are informed that other characteristics of "unhelpful thoughts" include their being *"distorted";*

"plausible" (if true, how is someone to know which thoughts to trust and which to distrust?), and "*difficult to switch off"*. The authors then inform participants that: *"Initially it can be difficult to detect your 'unhelpful' thoughts. After all we are not used to focusing on what we are thinking about"* (but the authors have just informed participants that these thoughts are *"difficult to switch off"*).

The Manual then moves on to "*What are thinking errors?"* and *"Why do I need to identify unhelpful thinking patterns?"* and participants are informed that they should *"stand back and dissect the thought"* so that they would be "*one step closer to coming up with helpful alternatives".*

It is striking that there is no room in this model for existing helpful thoughts, even though virtually every ME/CFS sufferer initially believed that they would improve and they continue to spend precious resources (financial and physical) seeking amelioration of their suffering. As is obvious from the internet, it is rare to find a patient with ME/CFS who does not strive to remain positive against overwhelming odds, but none of this is featured in the authors' own model, nor is it even acknowledged by Burgess and Chalder.

Participants are instructed on *"How to challenge your unhelpful thoughts"* by *"detecting possible thinking errors or distortions"* and by *"finding evidence that does not support them"*. Inevitably, participants must keep a "*new thoughts diary"* and are instructed that they must *"follow the guidelines carefully".*

Participants are given a list of *"Points to bear in mind when tackling unhelpful thoughts"* which include being told to *"remember that there is no right or wrong way of thinking"* (what then, is the point of this Manual? It has used endless pages informing participants that they have "*thinking errors").*

Section 2 ("*Tackling unhelpful assumptions and core beliefs"*) tries to modify participants' core beliefs and it exemplifies the unwarranted psychologisation of "CFS/ME".

The underlying assumption is that participants can recover once the "*blocks"* that reside in their thoughts and behaviour have been overcome by correct thinking, including correcting their *"personality traits"*.

"Below is a list of things that may be influencing your progress (all of which have been addressed earlier in the intervention):

"1. Fear about increased activity making you worse. Worry about …taking the risks that are necessary to help you overcome your CFS/ME" (participants are warned that they have to take risks to "overcome" their CFS/ME, yet they are assured that CBT and GET are safe; if so, why might they pose risks?).

"2. Having extremely high personal standards" (this informs the participant that being a perfectionist is a block to recovery; there is no proof that this is true, but it is stated as a proven fact and it might undermine the self-confidence of the participant); *"avoiding new activities"* (how does this block recovery from ME/CFS?).

"3. In receipt of benefits or a permanent health insurance" (participants are informed that they may feel trapped by their benefits or insurance policy payments into not trying hard enough to get better).

"4. Having another illness on top of your CFS/ME" (how does a participant distinguish between "real" pain caused by another illness -- and therefore "allowed" -- and the pain caused by ME/CFS that is to be ignored?).

"5. Conflicting advice or being in receipt of different kinds of therapy/diets. There are health professionals who would suggest that you need tests or should try different types of treatment, this can lead to confusion" -- this seems dangerous advice given by Burgess and Chalder (behaviour therapists who are not medically qualified): it not only tells the participant not to trust other health professionals but it dissuades participants from seeking medical care. This may be a serious breach of ethics.

"6. The 'wrong' kind of social support…Your relative may discourage you from doing more…If family members have been your carer during your illness, they can sometimes feel that they no longer have a role to play, which can sometimes lead them to be critical of your CBT programme and deter you from persevering with it" (this tells participants not to listen to family, but to obey the therapist, inviting the possibility that a family member may be guilty of Munchausen's syndrome by proxy).

"7. Cultural issues: some cultures have difficulty in accepting different kinds of illnesses, particularly if an obvious physical cause cannot be found. This may lead the person to have many 'unnecessary' tests" (how does the non-medical therapist know such tests are unnecessary? This seems dangerous and unethical and may be in breach of professional codes).

The next section (page 95) is titled "*Work, Courses and Resources"* (another indication that the PACE Clinical Trial is about getting people off benefits).

The authors clearly wish to be seen as friendly towards participants, so they suggest that *"some people are not aware that they are able to claim benefits"* and they list various basic benefits. They include Severe Disablement Allowance (SDA), yet this benefit has not been available to new claimants since 2001.

On page 111 the authors return (yet again) to "*Management of set-backs"* and inform participants that a set-back *"can be dealt with quite easily"* (this is inexcusable: where is the proof that a relapse can be dealt with quite easily? Professor Klimas is unequivocal: "*Certainly, pushing through can cause 'crashes' and the relapses can last for days, even weeks"* [New York Times, 15th October 2009]. There is significant evidence that Burgess and Chalder's advice is erroneous).

The authors then inform participants that set-backs may occur *"if you stop using the techniques described in this manual"* (this seems to be coercing the participant to obey the therapist, as it states that failing to follow the techniques in the Manual may cause relapse).

Burgess and Chalder also inform participants that if they have a temperature, they should increase their rest for a day or so, but that participants should *"not be tempted to rest for longer or until all your symptoms subside, as this may prolong your recovery"* (this seems dangerous, unproven and unethical advice from non-medical personnel).

Page 120 of the participants' CBT Manual lists "*Further reading"*, which is essentially "pop-psychology" and includes *"A woman in your own right"* by Anne Dickinson (Quartet Books, 1982); *"Overcoming low self-esteem"* by Melanie Fennell (Constable & Robinson, 1999); *"Asserting yourself"* by Sharon & Gordon Bower (Perseus Books, 1991); *"Overcoming anxiety: A self-help guide using cognitive behavioural techniques"* by Dennis Greenberger & Christine Padesky (Guilford Press, 1998); *"Feeling Good"* by David Burns (Avon Books, 1999), and Trudie Chalder's own book "*Coping with chronic fatigue"* (Sheldon Press, 1998) which tops the list.

The "therapeutic relationship" between participant and therapist which is central to the PACE Trial seems not to be authentic because it is contrived and predicated on misinformation and so is anything but "therapeutic". It is quite the reverse, discouraging autonomy and leaving people defenceless against the bias and indoctrination of the Wessely School. Indeed, it seems that the whole point of the CBT programme set out in the Participants' CBT Manual is to undermine the self-confidence of the participants. They are told not to listen to their own body; they are told they have thinking errors; they are told their life-style caused their illness and they are told that the way they have managed their CFS/ME has prevented them from recovering.

Is this the purpose of a clinical trial, or is it the propaganda of the mental health movement, whose aim is said to be *"to 'infiltrate the professional and social activities of (all) people'…via 'perception management'. Thanks to behavioural scientists, perception management is now pervasive….The Wikipedia definition adds the 'imposition of falsehoods and deceptions', seen as important to getting 'the other side' to believe what one wishes it to believe…(by)*

'Behaviour Modification' and 'Conditioning' and 'Re-education and Social Propaganda' " (Beverly Eakman: The New Face of Psychiatry. The New American, 13th October 2009). One commentator on Eakman's article noted: *"Learned helplessness is another angle they take, shocking us....repeatedly…until we are psychologically crippled"*. There will be few in the ME/CFS community who can forget what Professor Wessely wrote almost two decades ago about them: *"External attribution protects the patient from being exposed to the stigma of being labelled psychiatrically disordered, (affording) diminished responsibility for one's own health….Our results are close to those predicted by* ***learned helplessness****"* (J Psychosom Res 1990:34:6:665-667).

The purveying of misinformation to – and the withholding of pertinent biomedical information from -- PACE Trial participants in the CBT arm of the trial may be unethical and it suggests that either the West Midlands MREC was derelict in its duty (a matter for the Minister of State for Health) or was misinformed.

Quotations from the Therapists' Manual on GET

The Introduction to the 189 page GET Manual for Therapists states: *"This manual contains the information necessary to allow you to confidently apply Graded Exercise Therapy (GET) for participants with Chronic Fatigue Syndrome (CFS) / Myalgic Encephalitis / encephalopathy (ME)". It also covers some of the more subtle issues related to the therapeutic process, which if overlooked could result in non-adherence on the part of the participant".*

From the outset, for the authors not to get the name of ME correct indicates unacceptable carelessness, especially – as noted in Section 3 above -- concerns about inconsistent terminology were raised by Professor Darbyshire (Chair of the Trial Steering Committee) and minuted at the Joint Meeting of the Trial Steering Committee and Data Monitoring and Ethics Committee held on 27th September 2004 at which Professor Peter White was present. The Minutes record that the Trial Manager, Julia De Cesare, was to ensure consistent terminology, but this seems to have been overlooked.

Much of the content of this Manual is almost identical to the CBT Manual, ie. the importance of assuring the participants that the therapists believe they have a "real" illness, and the importance of maintaining *"warmth"*, "*empathy", "encouragement"* and *"sensitivity"*, the purpose of which being to ensure the subjects' continued participation and compliance, so these contrived affectations can only create an insincere relationship between the participant and the therapist.

Therapists are instructed on *"Engaging participants in GET"* and told that: *"encouraging them to undertake their exercise plans are cornerstones to your therapy. The following suggestions are likely to improve engagement and compliance with the programme: Ask what the participant would like to be called when you first meet; tell the participant that you look forward to working with them over the coming months".* There is emphasis on *"positive reinforcement"* and *"encouraging optimism"* and on "*How to structure treatment sessions".*

Therapists are also instructed that they must be sure to set up and switch on the recording equipment.

One notable point is that GET therapists are informed on page 14 that the essence of Standardised Specialist Medical Care (SSMC, received by all PACE Trial participants) is *"good quality medical care"* and that the medical advice to be given "***will be compatible with any therapy that the participant is receiving (APT, CBT, GET or SSMC alone)".*** This seems to mean that the doctor delivering the "SSMC" is placed in the invidious position of having to give advice based not on their clinical assessment or the participant's clinical need but on the Investigators' assumptions about whatever "therapy" the participant is receiving: ie. if the participant is receiving GET and experiences an exacerbation of symptoms, the doctor must reassure the participant that this is a normal consequence of using deconditioned muscles. If, however, the participant is on the APT arm of the Trial and experiences a worsening of symptoms, the doctor must tell the participant that they are doing too much and should rest more; **thus participants in the PACE Trial with identical symptoms are apparently to be given differing advice by a clinican that is solely dependent on the particular arm of the trial to which they have been allocated**. The Minutes of the Joint meeting of TSC and DMEC held on 27th September 2004 record: "*clinic doctors would be working within a remit of advice and medication they could give".* Is this ethical?

Page 23 of the Manual purports to explain to the therapist the model and rationale behind GET, which the authors state "*stems from both physical and behavioural understanding of CFS/ME".* The therapists are not informed that the "GET model" is only a hypothetical model and it is presented as fact. Therapists are told to *"re-visit the model frequently".* Frequent reiteration of "the model" without qualifying its theoretical status is misleading to both therapists and participants alike.

Throughout the GET Manual for therapists the emphasis is on "deconditioning", yet in their article in the Journal of Mental Health (2005:14:3:237-252), Lucy Clark and Peter White acknowledge that: "*We do not know whether this deconditioning maintains the illness or is a consequence".*

In their article, Clark and White aimed to review the literature relating to the role of deconditioning in perpetuating CFS and the literature relating to the role of graded exercise therapy as a treatment for CFS. They carried out a non-systematic review of published papers and concluded – perhaps inevitably – that *"supervised graded exercise therapy reduces fatigue and disability in ambulant patients with CFS"*. What is more surprising is that they also concluded that: ***"efficacy may be independent of reversing deconditioning"*** and that: *"Further work is necessary to elucidate the risks, benefits and mechanisms of such treatment*". Despite their conceding that more work is necessary to elucidate the risks, Clark and White asserted: "*Patient education is necessary to inform patients of the positive benefit/risk ratio in order to improve acceptance and adherence"*. Given that they admit that further work is necessary to elucidate the benefit/risk ratio, it is notable that they felt able to describe that ratio as ***"positive"*** and to rely on this alleged positivity to engender improved patient acceptance and adherence.

In their Manual for the PACE Trial the same authors state about graded exercise therapy: "***Physical deconditioning, exercise intolerance and avoidance caused by relative inactivity are reversed****…aiming to return a patient to normal health and ability"*. If GET can *"return a patient to normal health and activity"*, what is the purpose of this trial that is costing millions of pounds sterling? Furthermore, if GET can *"return a patient to normal health and ability"*, is it ethical to withhold it from participants receiving CBT, APT or SSMC alone?

The authors tell GET therapists that: *"Prolonged inactivity can perpetuate or worsen fatigue…in people recovering from a viral illness"*, the reference for which (number 15 in the Manual) is a study dating from almost fifty years ago (Postgrad Med 1961:35:345-349).

In their Manual for GET therapists, Bavinton, Clark and White state: "*Physical deconditioning is characterised by reduced muscle strength and aerobic capacity. This has been supported by a number of exercise studies that have shown reduced exercise tolerance in CFS/ME patient compared to controls.* ***Six of these studies found that people with CFS/ME were*** *either more deconditioned than healthy controls or* ***at least as deconditioned as sedentary healthy controls"***. This is remarkable, since the authors of this Manual here vitiate their own hypothesis, **because if some people with CFS/ME are only as *"deconditioned as sedentary healthy controls"*, then can CFS/ME be caused by deconditioning**?

Furthermore, the authors fail to mention the significant body of evidence showing that exercise could be harmful to some people with ME/CFS. Therapists ought to be made aware that such evidence exists in order to meet the ethical requirement to ensure that all research staff are competent. Therapists employed in an MRC trial might believe that they have a moral entitlement to know that they are delivering an intervention which, however skilfully administered, could cause significant harm to some participants.

The references cited in support of the authors' hypothesis which is the basis of the PACE Trial is mystifying because those references also vitiate the authors' hypothesis, for example, reference 22 in the Manual (Bazelmans et al. Psychol Med 2001:31:107-114) found that deconditioning was not a factor in ME/CFS.

Moreover it is notable that the authors of this Manual appear to misrepresent the findings of some of the studies they cite in support of their own beliefs, for example, they acknowledge that there was a *"negative correlation with physical activity"* in some studies upon which they rely, yet they turn this around and claim that the findings of those studies support their own hypothesis: *"….suggesting that deconditioning was important even in these apparently negative studies*", a conclusion not arrived at by the authors of those studies.

In his submission on behalf of St Bartholomew's Hospital Fatigue Service to the NICE Guideline Stakeholder consultation process (2006), Professor Peter White said about those severely affected by ME/CFS: "*We think it may be worth thinking about* ***one of the main aims of GET not being a particular amount of exercise, but more of a behaviour change – therefore for anyone at any level, GET aims to increase what they are doing by changing the way that they currently do things and then adding in something new"*** (Comments Table 6:297).

Bavinton, Clark and White discuss the more severely disabled group of "CFS/ME" patients on page 24 of the Manual and comment: "*Due to greater levels of inactivity in the more severely affected group, the deconditioning model should apply equally if not more to these patients"*.

This directly contradicts the submission of Professor Anthony Pinching of the Peninsula Medical School to the 2006 NICE Stakeholders' consultation process (Comments on chapter 6, page 202-203): *"This statement suggesting possible benefit of introducing GET to severely affected patients is extraordinary. There are no data to support it, and patient and clinical experience regularly reaffirm the inappropriateness and inapplicability of GET as such to patients with this level of disability"*.

Therapists are instructed that: *"a major objective for GET is to undertake the amount of exercise recommended for full health and prevention of disease"*. This objective is prematurely optimistic in view of the absence of evidence that GET is curative for ME/CFS. It also suggests that therapists are being actively encouraged to hold high expectations of GET, and such indoctrination does not accord with the therapists' requirement to put the safety of the participant above all else.

More questionable information follows: "*Exercise is well known to have positive effects upon…the maintenance of a healthy musculoskeletal system"*; whilst this may be true for otherwise healthy people, the opposite may be true for those with ME/CFS, a possibility not even mentioned by the authors of the Manual, even though Professor White is well aware of it.

In 2000, he published "Strength and physiological response to exercise in patients with chronic fatigue syndrome" (JNNP 2000:69(3):302-307) in which he stated: "*CFS is characterised by postexertional or persistent fatigue, with consequent disability. Until recently no abnormalities of muscle physiology or metabolism that could explain the fatigue had been reported* (an inexplicable assertion--- see the section on documented muscle abnormalities in ME/CFS in Section 2 above, which date from 1984). *Lane et al found an increased lactic acid response to exercise in 37% of patients with CFS and these patients were particularly likely to have type II muscle fibre predominance"*.

Undoubtedly, as an expert in "CFS/ME", Peter White will be aware of the work of Russell Lane, who published his findings of enteroviral related metabolic myopathy (JNNP:2003:74:1382-1386): ***"The findings could not be explained satisfactorily by the effects of deconditioning or muscle disuse***". Lane et al concluded: "***Further studies using phosphorus magnetic resonance spectroscopy have shown that some CFS patients have defective muscle energy metabolism, notably reduced ATP resynthesis rates following exercise, suggestive of mitochondrial dysfunction".***

As an expert, Professor White must thus have been aware before beginning the PACE Trial that a significant proportion of people with ME/CFS have *"defective muscle energy metabolism"*. For him to co-author (and, as Chief Investigator, to approve) a Manual that ignores such significant evidence seems to reveal a disturbing lack of rigour and a disregard for the profound suffering of patients with ME/CFS.

This is especially true given that the PACE Trial is jointly funded by the Department of Health, whose own Research Governance Framework for Health and Social Care, Second Edition, 2005, states:

"2.3.1: All existing sources of evidence…must be considered carefully before undertaking research".

Clearly that is not the case in relation to the PACE Trial because most of the large body of biomedical evidence about ME/CFS has been disregarded by the researchers.

Moreover, it appears that participants were not given the chance to decide for themselves whether or not to disregard this evidence, and possibly neither were the therapists.

Was the West Midlands MREC given the opportunity to decide if the withholding of such evidence was ethical?

The Governance arrangements for NHS Research Ethics Committees, 2001, state:

"9. The Process of Ethical Review of a Research Protocol

Elements of the review

9.7 The primary task of a REC lies in the ethical review of research proposals and their supporting documents, with special attention given to the nature of any intervention and its safety for participants, to the informed consent process, documentation, and to the suitability and feasibility of the protocol.

9.8 The Research Governance Framework makes it clear that the sponsor (in this case, Barts and The London NHS Trust, which is effectively Peter White) *is responsible for ensuring the quality of the science. Paragraphs 2.3.1 and 2.3.2 state:*

It is essential that existing sources of evidence, especially systematic reviews, are considered carefully prior to undertaking research. Research which duplicates other work unnecessarily or which is not of sufficient quality to contribute something useful to existing knowledge is in itself unethical.

All proposals for health and social care research must be subjected to review by experts in the relevant fields able to offer independent advice on its quality. Arrangements for peer review must be commensurate with the scale of the research."

9.13 Scientific design and conduct of the study:

b. the justification of predictable risks and inconveniences weighed against the anticipated benefits for the research participants, other present and future patients, and the concerned communities

9.14 Recruitment of research participants:

c. ***the means by which full information is to be conveyed to potential research participants or their representatives***

9.15 Care and protection of research participants:

a. the safety of any intervention to be used in the proposed research

*b****. the suitability of the investigator(s)'s qualifications and experience for ensuring good conduct of the proposed study***

c. any plans to withdraw or withhold standard therapies or clinical management protocols for the purpose of the research, and the justification for such action

9.17 Informed consent process:

a. ***a full description of the process for obtaining informed consent****, including the identification of those responsible for obtaining consent, the time-frame in which it will occur, and the process for ensuring consent has not been withdrawn*

b. the adequacy, completeness and understandability of written and oral information to be given to the research participants, and, when appropriate, their legally acceptable representatives".

In the section of the GET Manual for Therapists entitled "*Adverse effects of GET"*, the Manual's authors inform therapists that "*Surveys by patient groups of their members have suggested that GET may be harmful to some people with CFS/ME. It is now believed this finding was due to inappropriately planned or progressed exercise programmes, possibly undertaken independently or under supervision from a person without appropriate experience"*.

As noted in Section 1 above, a large UK survey found that there was no significant difference between the number of adverse reactions suffered by those who undertook a programme of GET under an NHS specialist (31.1%) compared with those who undertook such a programme elsewhere (33.0%). Although that particular survey was in 2008 when the PACE Trial was underway, other similar evidence exists (see Section 1 above).

In the 2007 published (abridged) Protocol, the PIs rely on responses to a 2003 questionnaire (AfME Membership Survey, 2003: "Your experiences"), stating "*A further survey by Action for ME of their members suggests that reports of deterioration with therapy are related to either poorly administered treatment of lack of appropriate professional supervision"*; however, when analysed, the results from the 2003 survey in relation to GET show that when administered by a physiotherapist, 67% had a negative response and 33% had a positive response and when administered by an occupational therapist, 100% had a negative response and 0% had a positive response. As Kindlon notes: "*One doesn't need to use any fancy statistics to know that the results from the 2003 AfME survey do not 'explain away' the high rates of adverse reactions to GET at all"* (Co-Cure RES, ACT: 5th February 2010).

Without participants being provided with such knowledge, their informed consent may not have been valid.

In the section "*Feeling Better With Exercise: The Cycle Of Reconditioning"*, the therapist is told to create a *"stable baseline of exercise"*, yet a person with ME/CFS may never manage this since -- unlike chronic "fatigue" -- their condition is by definition fluctuating.

Therapists are told that they must *"ALWAYS ensure…that every stage is jointly negotiated"*. How can participants negotiate in such a situation? The purpose of GET is incremental aerobic exercise, so the participant must push through symptomatic exacerbations, having been told that it is safe to continue. Moreover, as the therapist is instructed to ensure "*warmth"* and "*empathy"* in order to engender the participants' trust, a participant who trusted the therapist would be unlikely to do much negotiating, because they would want to be cured.

This Manual has the same instructions about tactics of "*Engagement"* as the CBT Manual for therapists, including not letting participants think that "it's all in the mind" --- "*Many of them will report at least one upsetting incident relating to a health professional, whether it is … not being taken seriously or being told it is all in their mind"* (but according to this model, it <u>is</u> "*all in their mind"*: the GET model is predicated on the basis that there is no pathology, only psychopathology – including enhanced interoception or symptom focusing, according to Professor White -- and flabby muscles).

White's views on interoception are unequivocal. In his Editorial in the British Medical Journal (BMJ 2004:329:928-929) he stated: "*Patients with chronic fatigue syndrome underestimate their cognitive and physical abilities, while being more aware of their internal physiological state, a phenomenon called* ***interoception***". White's assertion that patients with ME/CFS are "*more aware of their internal physiological state*" than he appears to think is reasonable, together with his statement that "*this enhanced body awareness or* ***interoception*** *may itself cause sedentary behaviour*" has been robustly challenged.

Patients with ME/CFS whose lives are wrecked by balance problems (including frank vertigo), recurrent pancreatitis, myocarditis, recurrent episodes of intense, crushing chest pain that are clinically indistinguishable from cardiac infarction, vasculitis, neuromuscular incoordination (including difficulties with swallowing and fine finger coordination, for example, doing up buttons, holding a pen or turning pages of a book), difficulty getting enough air into the lungs, incapacitating post-exertional exhaustion

(which is nothing like being "tired all the time"), intractable muscle pain and frequency of micturition, including nocturia, would indeed be psychologically disturbed if they were **not** appropriately and legitimately concerned about such distressing symptoms. The Wessely School, however, attribute such symptoms to somatisation disorder and dismiss or disregard the evidence showing that such attribution is unjustified.

It is unacceptable for such symptoms to be either dismissed or ignored by those who prefer not to accord them even minimal consideration, but regardless of the evidence of significant organic pathology, White concluded his Editorial: "*Treatments that 'reprogramme' **interoception** such as graded exercise therapy and cognitive behaviour therapy, seem to help most patients*". *"Most patients"* with ME/CFS, as distinct from those with chronic "fatigue", do not agree.

Inevitably, participants in the GET arm of the PACE Trial must, as those in the CBT arm, search for alleged "maintaining" factors (such as symptom focusing).

However, unlike the Therapists' Manuals for both CBT and APT, the GET Therapists' Manual encourages the therapist to go further, stating on page 35: "*You can explain **the previous positive research findings of GET** and show in the way you discuss goals and use language that you believe they can get better*".

Not only is it unethical for a therapist to convey to participants in a clinical trial that the therapist believes they can get better with the intervention being tested, but this seems to be at variance with what the therapist is told on page 78 of the same Manual: "*Difficult questions relating to the trial: Participant expresses doubt over GET. **Explain that there are no particular references you can recommend for GET***".

The section entitled "*Explaining the GET Model to Participants"* is described as the *"use it or lose it"* theory, with the benefits of exercise being extolled. Therapists are urged to: *"…tell them that…an increase in intensity will help further strengthen the body"*, an assertion that is pure speculation in relation to people with ME/CFS.

Therapists are instructed: *"Try to illustrate this using specific hobbies they have. For example, if working with a musician, draw parallels with GET theory with learning to play to a high level. You might explain how a beginner will need to start with practising musical scales, learning to read music and learning where to place their fingers on the instrument. They can then learn music to grade I level, practise at this level for a while before feeling comfortable trying grade 2. Such metaphors can be very powerful in getting a participant to understand the theory of deconditioning and reconditioning"* (would it be acceptable for this metaphor to be applied to people with multiple sclerosis and to suggest that they have lost their muscle strength because of inactivity?).

Therapists are told *"You can give them information on previous research trials of GET for CFS/ME that show increases in physical strength, fitness, and functional capacity"* (this should not occur in an on-going clinical trial – imagine the outcry if investigators testing a drug told some but not all participants that the drug was successful before the outcome of the trial was known). Furthermore, if GET has been proven to be curative, then the ethical standing of the PACE Trial would be in question, as the REC Guideline quoted above makes plain:

"9.8: Research which duplicates other work unnecessarily…is in itself unethical".

Therapists are taught that: *"The role of exercise in…the prevention of major chronic diseases, such as stroke…coronary heart disease…cancers can also be explained"* (in patients with ME/CFS exercise, especially incremental aerobic exercise, could in fact increase the risk of cardiovascular disease by promoting inflammation).

Therapists are also told that *"You can share with them the research that shows reduced numbers of mitochondria in muscles of people with CFS/ME and how this is related to reduced energy capacity in their muscles **as a result of too much inactivity***" (patients with ME/CFS do indeed have abnormal mitochondria, but it has not been proven

to be a consequence *"of too much inactivity"*; performing a muscle biopsy before and after the PACE Trial would have been a useful and objective measure of mitochondrial abnormality; even minimally invasive tests to measure lactic acid and mitochondrial function before and after GET would have been useful and objective measures of the efficacy of GET).

At this point, the therapists are taught about how the various sessions of "therapy" are to be implemented.

In Phase 1 (covering sessions 1-3), therapists must explain what is required of the participant; they must *"engage the participant in GET model and explain reversibility"* (ie. they are effectively promising a cure); therapists must carry out *"an assessment of motivation to exercise"*; they must carry out a "*brief physical assessment"*, but therapists are then told: "*objective measures and fitness assessment will already have been conducted prior to your assessment, and this data passed on to you. You will not receive any actigraphy data"* (another contradiction: *"objective measures will already have been conducted"* but "*you will not receive any actigraphy data":* the actigaphy data is the only objective measure, so why deny the therapists this information? Is the reason because Professor White decided that no actigraphy data for comparison will be obtained at the end of the trial?).

Therapists are told that: *"Participants will already have undertaken a thorough physical assessment"*. A short level walking test is far from a thorough physical assessment, and no serial testing was being carried out. A patient with ME/CFS may be able to perform an activity on one occasion but will typically relapse after a day or so, hence the need for serial testing. A one-off test cannot be considered objective, given the evidence of delayed response to activity seen in ME/CFS. The fact that the therapist is instructed to repeat the level walking test after one minute of recovery, when the heart rate and Borg Scale are to be repeated, is of doubtful value in patients with ME/CFS, especially as the correlation between the Borg Scale and the heart rate is known to be weak in any case, yet this appears to be the main "objective test" in the trial.

Much space is devoted to the Borg - HR (heart rate) relationship, apparently without understanding that it may have little application for people with ME/CFS. The Borg Scale has been shown to be higher in people with ME/CFS than in controls.

The Borg Scale is used by sports coaches and by personal trainers to measure athletes' and body-builders' levels of intensity in training; it measures perceived exertion. In medicine, it is used to document the patient's exertion during a test and includes a measure of breathlessness in relation to heart rate (HR).

Still in Phase 1, therapists are taught that: *"The main purpose of engaging the participant in the model is to allow the participant to understand the multifactorial influences exercise can have on their health* ***and CFS/ME recovery****"* . It is not ethical in a trial to tell the participants in one arm of the trial that the "treatment" they are receiving **can lead to recovery**. The participants have a right to know that people who have undergone GET have been made severely and permanently worse by it (see Section 1 above).

The therapist is next taught about "*boom and bust"* patterns of behaviour which the authors assert occur in participants: *"over activity may lead to an increase in rest and a decrease in fitness and function if prolonged".*

Unfortunately, the authors' explanation is illogical. Assuming (i) that the participant is in a "boom and bust" pattern of activity and (ii) that the deconditioning hypothesis is correct, then after every "bust", the person would deteriorate and not return to their prior level of fitness, ie. for the assumptions to be correct, one would expect to observe progressive deterioration in all ME/CFS patients, but this is not the case, hence one of these assumptions is incorrect.

The therapists are informed: *"Many people with CFS/ME find…there is a significant post-exertional response"* (all people with ME/CFS experience a post-exertional response: if they do not exhibit this cardinal feature of ME/CFS, then they do not have ME/CFS and should not be in the PACE Trial).

The therapists are taught about the importance of "*set goals*": "***A goal for GET should be a clearly observable behavioural change, not a reduction or absence of a symptoms*** (sic)". The participant has already been told that recovery is possible, yet the goal is not to make the patient feel better, but to make them more active -- once again, it brings to mind UNUMProvident's **"Chronic Fatigue Syndrome Management Plan"** referred to in Section 3 above: ***"Attending physicians (must) work with UNUM rehabilitation services in an effort to return the patient / claimant back to maximum functionality with or without symptoms".***

"Long term goals (six months or longer)" are suggested to include: "*riding an exercise bike for twenty minutes every day; managing to vacuum the home all in one go; swimming 20 lengths three times a week"* (anyone able to do this is likely to have been wrongly diagnosed).

Therapists are informed that: "*By week 4, most participants will be able to commence aerobic exercise"* and that the aim is to achieve *"as soon as possible five or six aerobic sessions per week"*. Anyone suggesting this regime does not understand the disease ME/CFS.

Phase 2 (*"Active Treatment"*). Therapists are told that: *"Graded exercise treatment follows the basic principles of exercise prescription for healthy individuals, but adapted to suit the participant's current capacity. The exercise therapy should have two components: stretching and aerobic conditioning"*. Aerobic exercise must *"Start and remain at 5 – 6 days out of 7"*.

Therapists are instructed that the importance of "*negotiating a sustainable baseline of aerobic exercise cannot be overestimated"*. Participants are to be told that they should *"expect a mild increase in fatigue or muscle stiffness / soreness as a normal response to exercise"* (this is not necessarily *"a normal response to exercise"* -- it could equally be a pathological response to exercise, but neither the therapist nor the participant is to be warned about such a possibility).

Therapists are told that *"some participants may not be motivated by a specific strengthening programme, and can be encouraged instead to participate in functional strengthening exercises, e.g. cleaning high cupboards"*. Is cleaning a high cupboard an appropriate intervention in an MRC clinical trial?

If a participant is *"keen to aim towards a goal that is beyond their current capability"*, the therapist must "*discuss how they could increase their physical exercise to achieve their plan. For example, if the participant wishes to attend a local kick-boxing class* (sic), *they will need to build up their aerobic capacity to be able to achieve an hour of high intensity activity"* (any person who can even consider attending a kick-boxing class for an hour has no right to be in the PACE Trial, as they certainly do not have ME/CFS or even "CFS/ME", which is the disorder the Investigators claim to be studying).

Next comes consideration of *"Preventing and managing setbacks"*. Therapists are told that: *"CFS/ME setbacks usually involve an exacerbation of their symptoms. Participants may describe these as a 'relapse' "* (it is unclear what kind of relapse does <u>not</u> involve an exacerbation of symptoms).

"People with CFS/ME can usually identify an increase in physical activity which may have attributed (sic) *towards their setback"* but the therapist is quickly told that: "*it is unlikely to be the exercise programme that is responsible"* (how can the therapist know this? This is a potentially dangerous assumption).

However, the therapist is told that: *"A central concept of GET is to MAINTAIN exercise as much as possible during a CFS/ME setback. This is to reduce the many negative consequences of rest…Some participants may be resistant to this approach…Additional support may be required at this time"*.

In the section "*Encouraging a good night's sleep"*, the therapist is informed that: "*exercise improves sleep"* (where is the evidence that this assertion is true for people with ME/CFS? The two references cited [numbers 39 and 40 in the Manual] do not relate to people with ME/CFS; one of them relates to female shift workers).

Phase 3 (page 54 of the Manual) is titled *"Ending of treatment, preparing and planning for future self-management"*. Therapists are told that the purpose of Phase 3 is three-fold: *"1. To aim towards self-management and independence with exercise programme; 2. To re-examine the Borg- HR* (heart rate) *relationship; 3. To examine how to maintain exercise after discharge"*.

The therapist is informed that "*Exercise target heart rates are calculated for each individual"* and two methods are described; therapists are told that *"The main difference between method 1 and method 2 lies in the resting heart rate (RHR)"* and that method 1 uses *"a calculation known to therapists / gymnasiums, and aiming for a normal heart rate target"*, whilst method 2 is *"as used in previous CFS/ME research"*. Therapists are informed that method 1 does not take the RHR into account and is simpler to use and that *"It is therefore advisable to use method 1 to start with"*.

Therapists are told that: "*as a lower intensity workout for a longer duration is both more comfortable and is recommended for improving overall fitness, 60 – 75% of Max HR can be used as a guide. As this figure is used for normal, healthy people and is not adjusted for CFS/ME, the objective is to work up to this figure gradually as the participant recovers"* (this assumes that the participant <u>will</u> recover with the intervention, but until the outcome of the trial is known, this is speculation promoted as fact).

It is potentially dangerous to assume that a target that is appropriate for healthy people is also appropriate for people with ME/CFS (see the section on cardiovascular abnormalities in Section 2 above). People with ME/CFS often have a much faster heart rate, even at rest: it has been demonstrated that they have an increased resting energy expenditure (REE).

For example:

(1) "*Chronic Fatigue Syndrome is a clinical disorder that is increasingly recognized in most countries as a major health hazard. Its classical clinical feature is fatigue associated with sleep abnormalities, difficulties concentrating, memory impairment and myalgia"*

*"**To this may be added a constellation of other symptoms, including atypical chest pain, gastrointestinal motility disorders, unexplained attacks of sweating and light headedness. The fatigue is clinically identical to that found in multiple sclerosis, Parkinson's disease, Alzheimer's disease, post-polio syndrome and the fatigue that may follow posterior head injury"***

"Abnormalities in muscle, neuromuscular transmission, heart and resting energy expenditure have been found in patients with (ME)CFS"

"These abnormalities may well be secondary to a primary abnormality of central cholinergic transmission"

"We tested this hypothesis using a neuroendocrine challenge paradigm (and) have shown that the pathogenesis involves up-regulation of post-synaptic cholinergic receptors". (A Chaudhuri T Dinan et al. Chronic Fatigue Syndrome: A Disorder of Central Cholinergic Transmission. JCFS 1997:3(1):3-16).

(2*) "When individual resting energy expenditure (REE) was predicted on the basis of total body potassium values, 45.5% of the (ME)CFS patients tested had resting energy expenditure above the upper limit of normal, suggesting that there is upregulation of the sodium-potassium pump in (ME)CFS.*

"There was no evidence that the results were due to lack of activity (which would have affected total body water estimates)" (Watson WS, Chaudhuri A, Behan PO et al. Increased resting energy expenditure in the chronic fatigue syndrome. JCFS 1998:4:4:3-14).

Therapists are advised that pedometers may be used *"where appropriate….you may find that a participant will be motivated by seeing the distance they are walking daily…and you may choose to use this as an adjunct to GET"*. However, therapists are then told: "*it is useful to discourage excessive attention to the figures displayed"*.

Having discussed the need for the participants to use an *"Exercise Diary"*, the authors return on page 63 of the Manual to the Borg Scale: *"It is normal for CFS/ME patients to have higher Rating of Perceived Exertion (RPE) or Borg Scale number than normal subjects. This may be related to sleep disturbance, deconditioning, enhanced interoception (increased awareness of body sensation) or mood disturbance"*. The reference cited for this statement is Peter White's own 1997 study (BMJ 1997:314:1647-1642). There is no mention that it could be related to physical disease such as described in Peter White's own 2004 study: *"The pro-inflammatory TNFα is known to be a cause of acute sickness behaviour, characterized by reduced activity related to 'weakness, malaise, listlessness and inability to concentrate', symptoms also notable in CFS"* (JCFS 2004:12 (2):51-66).

Therapists are then informed that: "*After an exercise programme, research has shown that the RPE* (Rating of Perceived Exertion) *in CFS* (no mention of ME here) *is normalized"*, the reference again being Peter White's 1997 study.

Therapists are told that: *"The sense of effort is not a reliable indication of physiological effort in a patient with CFS/ME. So the HR* (heart rate) *can replace this"*.

In the section in which the therapist is instructed how to carry out testing of the participant's heart rate, the instructions say: "*Heart rate will be recorded to objectify* (sic) *effort and fitness at the beginning, end, and at recovery"*, which once again instils into the therapist the idea that "recovery" is possible, an assumption that is not borne out by the evidence and in any case is the hypothesis that is allegedly being tested in the PACE Trial.

Therapists are also told that if the participant reports an increase in fatigue as a response to a new level of exercise, *"they should be encouraged to remain at the same level for an extra week or more* (this could be potentially dangerous for people with ME/CFS). *They should be reminded that each new level will initially feel harder until the body adapts"* (this is an assumption that the body can adapt, which may not be true for people with ME/CFS).

In the section titled *"Strategies for planning exercise"*, the therapist is exhorted to use "*motivational techniques…to improve compliance"* but such techniques must not involve CBT; therapists are advised that: *"using written reminders and rewards can also be helpful"* (are participants being bribed into compliance by the use of "rewards"?).

Therapists must encourage "*participation from partners, family and colleagues* (the use of the word "colleagues" means that the participant must be well enough to be employed). The therapist is advised to *"use a motivational technique known as motivational interviewing: ask the participant 'What is the likelihood of you undertaking this plan? (scale 1-10)'. If it is under 7, it is unlikely that they will do the activity being discussed, so it will need re-negotiating"*.

In the section "*Maintaining exercise"*, the therapist must explain that: "*in order for the body to continue strengthening, and for changes to be maintained, exercise should form a regular part of their lives from here onwards. The long-term benefits of exercise* ***for the prevention of CFS/ME specifically****, and other diseases in general can be emphasised"* (where is the evidence that exercise <u>prevents</u> "CFS/ME"?).

Therapists are taught that it is essential that *"the three supplementary therapies are as different as possible. In contrast to CBT, it is important that you do not consciously provide cognitive interventions, e.g. suggest that being able to exercise more may mean that there cannot be a persistent viral infection in their body* (but it is implicit that if it is safe to build up a level of exercise to that of healthy people, then the participant cannot have an on-

going viral infection); *should a participant speculate in this way you should remain non-committal…This is not the same as responding to a participant's questions about the therapy and providing educational explanations as to how and why GET works and how it is applied. This is allowed and is in fact imperative".*

The therapist is taught that: *"in contrast to APT, it is important that the 'envelope theory' of pacing is not adhered to.* ***APT is underpinned by an organic disease model*** *which encourages a person to stay within the limitations set by their illness, and being directed by their symptoms as guides to what they can do. The rationale of APT involves the ability of the body to heal itself by not provoking symptoms. In significant contrast, GET encourages the participant to stretch the limits of physical capacity in order to improve them"* (here, again, is acknowledgement that GET is not underpinned by an organic disease model).

Notably, therapists are advised that *"if a participant already attends a gym and follows a gym-based programme, they will not need to undertake the PACE strength exercises"* (how many participants are already attending a gym and following a gym-based programme? If a participant is doing so, then what are they doing on the PACE Trial? To include such people in the PACE Trial and compare them with people with ME/CFS seems to make a mockery of scientific integrity.

In the section "*Troubleshooting"*, the therapist is given guidance about "*Adherence or compliance problems: Participant wishes to terminate therapy or trial"* and is advised: "*In the first instance, you will contact the participant by telephone to ascertain the reason for drop-out…and establish whether any concerns can be resolved. This information should then be discussed with both the SSMC doctor and the centre leader. If the participant does not wish to talk to the physiotherapist or SSMC doctor, the centre leader or nominee should contact them themselves".* Given that participants have been assured -- in writing -- that they can leave the trial at any time without giving a reason, this looks like coercion to stay in the trial (and such coercion is said by participants to take place – see Section 3 above).

General advice to the GET therapist includes: *"it is best to use the language that the participant does to describe their symptoms. For example if a participant called there* (sic) *illness ME don't attempt to challenge this, ME or CFS is an appropriate term to use".*

Here is evidence that people with the WHO classified neurological disease ME are deemed to be included in the PACE Trial, in which case it is inexcusable for the authors and Investigators to have so blatantly disregarded the evidence-base pertaining to it and to have re-configured it as a somatisation disorder that is at the heart of the "GET model": the Investigators believe that participants do not have a physical disease, but that they have an abnormal perception of effort and have become deconditioned as a consequence. Nothing could be further from the truth.

Therapists are advised that if participants are *"insistent that there is an ongoing 'physical' problem…it is important that you acknowledge that their illness is real but its effects can be reduced by the way they manage it"* (this is misleading: the effects of ME/CFS – as distinct from chronic "fatigue" – cannot be ameliorated by the way it is managed: over 3,000 people struggling to cope with life-wrecking symptoms which do not feature in the PACE Trial models of "CFS/ME" have first-hand experience that this is untrue – see Section 1 above).

It is an affront to people with ME/CFS for the authors of the GET Manual for Therapists to refer to the intractable pain that is the daily burden of so many people with ME/CFS that cannot be controlled even with opiates as "*muscle soreness. Some people describe this as a pain, or as a heavy or stiff feeling, or a muscle tension"*; to do so indicates no understanding of the reality of ME/CFS. It is notable that in 1990, Trudie Chalder (to whom specific acknowledgement is made by the authors of this Manual) referred to "***the profound muscle pain that characterizes the syndrome"*** (Brit J Gen Pract. February 1990:82-83). People have been driven to suicide because they could no longer tolerate the intense and intractable pain of ME/CFS (http://www.meactionuk.org.uk/Background_Information_re_CBT.htm).

Simply by excluding those who are severely affected by ME/CFS from the PACE Trial does not mean that they do not exist, and for the Investigators to subsume "ME" into their own behavioural model of "CFS" seems to perpetuating the iatrogenic abuse to which such people have been subjected for over two decades. The PACE Trial Principal Investigators bear responsibility for the trial's potential impact on the severely affected: as noted above, the Governance requirements for NHS Research Ethics Committees, 2001, draw attention to:

" 9.18 Community considerations:

a. the impact and relevance of the research on the local community and on the concerned communities from which the research participants are drawn".

The impact that this research is likely to have on people who are severely affected with ME/CFS required full consideration before ethical approval was given. Although there appears to be intent to select participants who meet only the loosest criteria, have not been ill very long and are not very incapacitated, the effect of the research on other people with included diagnoses but much more severe illness must be considered.

Research is definitely not therapy (Adil Shamoo; Medscape Journal of Medicine 2008:10(11):254). However, the PACE Trial Manuals repeatedly refer to the "*treatment"* that is being delivered in the PACE Trial, and quite certainly, on 28th April 2008 Professor Peter White stood up at the Royal Society of Medicine and proclaimed GET as a safe and effective "*treatment"* <u>while the PACE Trial was still in progress</u>.

These are serious ethical considerations that seem to have escaped the PACE Trial Manager (Julia De Cesare) as well as the MRC Data Monitoring and Ethics Committee and the West Midlands MREC.

Quotations from the Participants' Manual on GET

This 142 page Manual for participants allocated to the GET arm of the PACE Trial warns them on every page that they must not reveal to anyone the contents the Manual: "*This information is intended only for the person to which is has been given for the purpose of undertaking GET for CFS/ME, and should not be shared, copied, or published in any way without permission"*.

At the same time, however, participants' families and friends are co-opted to share the same views as the therapists (ie. to become "co-therapists"). This effectively closes the exits for participants because family and friends are urged to adopt the beliefs of the Investigators, for instance by repeatedly asking the patient: "when are you going for a walk, where are you going for a walk, and who are you going with?", thus putting relentless pressure on the sick person. This sounds like the practice used by cults to brainwash their captives.

This Manual is equally as disturbing as the Manual for CBT participants, and unproven claims are made for the curative properties of GET, for example:

page 28

"In previous research studies, most people with CFS/ME felt either 'much better' or 'very much better' with GET."

"*Research has now shown that carefully graded exercise (Graded Exercise Therapy) can also be a very helpful therapy for CFS/ME."*

page 83

"It can be useful to keep setting yourself goals and challenges to focus your ongoing recovery after you have been discharged."

pages 109 & 110

"As long as a good balance of activity and rest is maintained, ***then recovery will be sustained****."*

Such claims do not accord with the evidence of more than 3,000 patients (see Section 1 above), nor with the biomedical evidence (see Section 2 above) and such overt influencing of participants in one arm of an ongoing trial may destroy the equipoise of the trial by "stacking the decks" in favour of the intervention known to be preferred by the PIs; moreover, there is no guarantee of recovery with GET so it is unethical to tell patients otherwise.

Since there is considerable overlap of the same misinformation in the CBT and GET participants' Manuals, this section will address only the more disturbing misrepresentations.

On page 10, the authors list "*Factors that may contribute to the development of CFS/ME"*, which is identical to page 6 of the CBT participants' Manual with one exception: the CBT participants' Manual lists "*Personality"* as an additional potential cause. In the PACE Trial, the alleged aetiology of "CFS/ME" thus appears to be elastic in that participants are given a different explanation about causation that is tailored to fit the assumptions of the particular therapy they are receiving.

On page 11 the authors state: "*Maintaining factors are important in CFS/ME because they give us clues as to the current problems* ***that are stopping you from getting better****"*. This last sentence does not appear in the CBT participants' Manual and is notable for a number of reasons. It states about "*maintaining factors"* that:

- they exist, which is assumption stated as fact

- they have prevented the participant from recovering, which is another assumption

- when they have been identified and changed, the participant will get better, which again is supposition.

It is not ethical to mislead trial participants in this way.

Pages 13 – 24 of the GET participants' Manual on *"Physiological Aspects of CFS/ME"* and *"Autonomic Arousal in CFS/ME"* are almost identical to pages 9 – 16 in the CBT participants' Manual, but with some inconsistencies.

On page 14 the authors assert: "*GET can help by building muscle strength, which allows you to do more"*. Even although GET is promoted in the CBT participants' Manual, this particular claim does not appear. Such a claim in relation to people with ME/CFS is unevidenced and unwarranted.

In the GET participants' Manual, the authors state: "*Due to changes in metabolism and other adaptations to bodily rhythms following prolonged rest, changes in the perception of body temperature may occur"* but the CBT participants' Manual says about the same issue: "*Due to changes in the blood volume and circulation following prolonged rest, changes in superficial body temperature occur"*; thus GET participants are told they they have a *"perception"* of change in body temperature, but CBT participants are told that there is an objective change.

In relation to "*Visual and hearing changes"*, the GET participants are told that there is *"a change in the way the brain perceives external sensations like noise and light, with consequent sensitivity"*, whereas the CBT participants are told that *"prolonged rest results in a 'headward' shift of bodily fluids"* and that it this " *'headward' shift of bodily fluids*" that is responsible for photophobia and hyperacusis, an assertion which, as noted in Section 3 above, is pure speculation by the authors.

In relation to reduced tolerance to activity or exercise, GET participants are assured that *"GET can help your ability to undertake physical activities"*, which is a declarative but unproven statement to participants that GET will help them.

Concerning *"changes in the central nervous system"*, GET participants are told that: *"One of the functions of the nervous system is to co-ordinate our muscles. GET can help by challenging your body physically, which can lead to improved co-ordination and balance"*. Once again, this is a direct statement to participants that GET will help them. Given the significant evidence of muscle abnormalities that have been documented in ME/CFS (see Section 2 above), such a claim cannot be justified.

In relation to *"Changes in mental functioning"*, GET participants are told that: *"Excessive rest may even affect the way our brain cells make connections with each other"* (notably, a claim that does not appear in the CBT participants' Manual) and they are told that: "*GET has been shown to improve mental functioning"* which, again, is a direct statement to participants that GET will help them, even though the alleged objective of the on-going PACE Trial is to determine whether or not GET <u>is</u> helpful, so Professor White and his co-authors are essentially pre-judging the outcome of the trial.

Sections in the GET participants' Manual relating to *"Alterations of the biological clock"*; *"Disturbance of cortisol production"*; "*Disturbance of the sleep-wake rhythm"*; *"Blood flow is altered"*; *"Muscle tension"* and *"Sweating"* are essentially the same as in the CBT participants' Manual, but an extra claim is made for the efficacy of GET, which is alleged to afford *"a way of dealing constructively"* with dysautonomia, a sweeping claim that is entirely unsubstantiated in patients with ME/CFS.

Next comes a long section on the benefits of exercise and its positive effect on the cardiovascular system as well as on muscle strength; muscle endurance; muscle flexibility; balance; the immune system; sleep;

increase in bone density; thinking ability (cognition); well-being and mood; weight loss; body image; confidence and "*social contact"*.

There is no acknowledegment or even recognition that participants may be experiencing many of the abnormalities illustrated in Sections 1 and 2 above, or that aerobic exercise may be actively harmful for people with ME/CFS.

It is unethical for therapists to tell trial participants that the intervention they are receiving in an on-going clinical trial is beneficial and, whilst true for healthy people, it may not apply to people with ME/CFS.

Next comes a section that further extols graded exercise therapy (GET), and the authors do not hesitate to use emotional manipulation, for example: "*If you would love to be able to walk your children to school…GET helps you to gradually build up your strength and fitness to achieve this"*. It is unacceptable to make such a definite promise of improvement to someone with ME/CFS.

There is a further litany of the alleged benefits of GET (already addressed by the authors, but therapists are taught that they must always provide "*positive reinforcement"*): "*In previous research studies most people with CFS/ME felt either 'much better' or' very much better' with GET"*; yet again, it is unethical for therapists to be telling participants in one arm of a clinical trial that they can expect to feel very much better with the intervention they are receiving, but the Principal Investigators seem to encourage exactly this with their insistence that there must be constant "*positive reinforcement"*, which might be deemed to be "brainwashing" participants.

This "brainwashing" (*"positive reinforcement"*) runs throughout the Manual, for example, participants are beguiled by the authors: "*You may be aware that the Chief Medical Officers Report of 2002 recommended GET as one of the most effective therapy strategies currently known"*. Not only did Peter White and Trudie Chalder refuse to sign the CMO's Report, but the authors of this Manual are co-opting the authority of the CMO's Report even though they did not agree with it. Referring to the CMO's Working Group Report in this way implies Establishment approval of the idea that GET is effective for "CFS/ME" when to ascertain this is an alleged objective of the trial.

How could the various ethics committees have approved such unethical weighting in one particular arm of an MRC clinical trial, especially given the evidence that this particular arm of the trial is well-known to be particularly favoured by the Principal Investigators?

Without doubt, the MRC Data Monitoring and Ethics Committee saw these Manuals, as did the West Midlands MREC (the latter having provided them under the FOIA).

It seems unlikely that the various ethics committee members ever read the Manuals, alternatively it seems unlikely that they read them with due care and attention.

Were ethics committee members derelict in their duty or expediently compliant? Ultimately, however, responsibility for the Manuals rests with the Chief Investigator, Professor Peter White, and it would ill-behove him to side-step his own responsibility by seeking to transfer accountability to the West Midlands MREC.

In the section "*Can exercise make me worse?"* participants are reassured that: "*You will be working with experienced physiotherapists* ***who have been well trained in the application of exercise to CFS/ME****"*. Who, apart from the Wessely School, trained these *"experienced physiotherapists"*? How can it be justified to describe such physiotherapists (who seem to have been recruited from a general physiotherapy background) as experienced and well-trained in the application of exercise to people with "CFS/ME", let alone to those who may have genuine ME?

Who taught the PACE Trial physiotherapists about exercise-induced oxidative stress; about the exercise-induced rise in isoprostanes; about TNFα; about channelopathies; about measuring C-reactive protein; about apoptosis; about cellular hypoxia; about abnormal T-wave inversion; about an abnormal augmentation index; about increased vascular stiffness and resistance and about receptor activity, and where is the evidence of their knowledge of and expertise in these areas?

GET participants are told that they will be setting goals jointly with their physiotherapist and will "*negotiate an initial activity with your therapist…the purpose is to challenge your body slightly so that it strengthens…Once this can be done consistently…the time you do this activity can be increased slightly…Our bodies tend only to be happy with increases of around 20%".*

How can an activity increase of *"around 20%"* apply to ME/CFS patients who already struggle with the basic activities of daily living? How can such people safely add any more aerobic activity to their life? **If such patients were excluded from the PACE Trial, then the results of the PACE Trial cannot be taken to apply to such patients.**

Participants are told that: *"Getting started might be difficult, possibly creating manageable feelings of stiffness or fatigue* ***as a normal physiological response to activity.*** *After a few days of maintaining activity at this level, these responses subside as the body adapts and strengthens".*

This is another assumption stated as fact. The stiffness or fatigue may not be a "normal" physiological response to activity for participants; the responses may not subside (they may worsen) and the body may not adapt and strengthen --- it may become more inflamed. These statements are predicated on the assumption that there is no underlying pathology; participants should be made fully aware of this, because the assumption is not evidence-based and has been shown to be erroneous.

On page 30 of this Manual the authors tell GET participants that their physiotherapist "*will use a heart rate monitor, which is an objective measure of how hard you are working"*. This is unacceptable; a heart rate monitor is not *"an objective measure of how hard you are working"* – it is an objective measure of how fast the heart is beating, which is entirely different. As noted above, the REE (resting energy expenditure) has been shown to be significantly increased in people with ME/CFS, and this affects the resting heart rate, so merely measuring the heart rate provides no evidence whatever of how hard a person with ME/CFS is working.

A recent paper (Miwa K et al. Internal Medicine 2009:48:1849-1854) noted that, unreasonably, little attention has been paid to cardiovascular involvement in (ME)CFS patients, even though frequent symptoms include shortness of breath (32%); dyspnoea on effort (28%); **rapid heartbeat** (38%); chest pain (43%); fainting (43%); orthostatic dizziness (45%) and coldness of feet (42%). The authors intensively investigated cardiac function in a cohort of ME/CFS patients (CDC 1994 Fukuda criteria) and demonstrated impaired cardiac function with low cardiac output and abnormalities in heart sounds. They also demonstrated pretibial pitting oedema (25%) and mitral valve prolapse (15%). Electrocardiograms showed severe sinus arrhythmia (34%) and vertical or right axis deviation, suggesting parasympathetic predominance. Stroke volume indices and cardiac indices were all lower in patients than in control subjects. The authors noted that epigastric splash and right kidney palpability, together with cold feet and pretibial pitting oedema, may be related to visceral ptosis and peripheral circulatory impairment, and that weakness, **rapid heartbeat** and orthostatic dizziness may be related to hypotension and orthostatic dysregulation. Notably, cardiac function fluctuated during exacerbation and remission phases, suggesting a direct relationship between severity and impaired cardiac function in ME/CFS patients. Although this paper post-dates the Manuals, there are similar papers that pre-date them, so there can be no excuse for the authors of the Manuals to have ignored this evidence that is so relevant to the PACE Trial.

However, GET participants are told that: *"weeding, cleaning, or washing floors or windows can be one of the best ways of regaining strength"*; again, this assumes that the muscles (the heart being a muscle) of a person with ME/CFS are normal, which has repeatedly been shown not to be the case.

The authors summarise their advice as follows: *"**There is nothing to stop your body from gaining strength and fitness…**"*; **this is misinformation and is dishonest, dangerous and unethical; neither the authors of the GET Manual nor the therapists can know this since appropriate investigations have not been carried out on PACE Trial participants as part of the trial, and moreover it is untrue, as shown by the evidence in Section 2 above.**

Next come various diagrams "explaining" the "*GET model*" and *"Feeling better with exercise"*, which claim that GET leads the body to "*adapt positively*" and so leads to *"improved strength, fitness, flexibility, endurance, achievement and focus"*.

There is no mention of even the possibility that participants with ME/CFS may be <u>unable</u> to benefit from aerobic exercise.

In the section *"The Role of Your Physiotherapist"*, participants are told that the physiotherapist's job is to *"explain how GET helps people with CFS/ME"*, but there is no evidence that GET does help people with ME/CFS and it may <u>not</u> help. The physiotherapist's job in the PACE Trial is also to "*Encourage you to maintain your positive gains"*; this implies that "*positive gains"* will not only have occurred but will also be maintained, when neither may be achievable for people with ME/CFS.

Such "*positive reinforcement"* may have the effect of blaming the participant who is unable to meet these set goals and it may well result in despondency and in a sense of failure.

The next stage in the GET Manual covers *"Getting to know the paperwork"* and includes admonitions about the need for the *"Exercise questionnaire; goal sheets; physical activity and exercise diary; GET plans and progress sheets; exercise records"* etc. Participants are given more "*positive reinforcement*": "***These sheets can be a powerful reminder of your progress".*** There is clearly to be no toleration of a <u>lack</u> of progress by any participant in the GET arm of the trial.

GET participants are next invited to express any concerns they may have about undertaking exercise. They are to be asked:

"*Apart from improving your **chronic fatigue*** (sic), *what other benefits of exercise interest you?"* and fourteen extra (guaranteed) benefits of exercise are listed.

Not only do the authors refer to ***"<u>chronic fatigue</u>"*** (which has nothing to do with ME/CFS), but this section is structured in such a way as to be a statement, not a question, as no-one could credibly answer negatively about any of the following fourteen guaranteed benefits of GET:

"*improved sleep; improved ability to do more activity; improved immune system; weight loss / control; prevention of osteoporosis; a healthier heart; improved breathing / less breathlessness; improved body image and confidence; ability to exercise with children / family; ability to exercise socially; feeling better in spirits; greater stamina; greater energy; greater strength".*

This is followed by an example of a "CFS/ME" GET participant's *"Physical activity and exercise diary"*, which includes:

"MONDAY: 07.00: Woke up; shower, breakfast. 08 00: Dropped kids off at school. 09.00: Breakfast (sic – apparently a typical CFS/ME participant on the GET arm of the trial has two breakfasts). *Walked dog 15 minutes. 10.00 – 12.00: on computer. 12.00 Lunch. 13.00: visit from friends. 16.00: pick up kids from school. 17.00: TV. 18.00: TV. 19.00: Dinner. 20.00: TV. 21.00 TV. 22.00: Bed.*

"TUESDAY: Woke up; shower. 08.00: Breakfast. Walked dog 15 mins. 09.00-12.00: Work. 12.00: Lunch. 13.00 – 17.00: Work. 18.00: TV. 19.00: Dinner. 20.00: TV. 21.00: TV. 22.00: Bed".

The illustrative diary provided for a GET PACE Trial participant for Wednesday includes walking the dog; then working a full day from 9am – 5pm, and additionally from 9pm to 10pm it includes*"household jobs"*; for Thursday, the diary includes walking the dog and then working from 9am – 5 pm, followed by an hour on the computer and then an hour of *"household jobs"*; for Friday it includes "*dropped kids off at school, walked dog 15 mins; household jobs* (10am – 1pm); *visited parents; pick up kids from school"*, followed by an evening watching TV from 5pm until 10pm; on a typical Saturday the "CFS/ME" participant takes *"kids to sports"; Sainsbury's"* and at 5pm takes *"kids to movies"*, with an hour watching TV from 9pm – 10pm; a typical Sunday includes "*take kids to park"*, "*out for lunch"*, *"walked dog with husband"*, then watching TV from 5pm to 10pm, including having dinner. The diary timetable shows very clearly that this "typical" PACE Trial participant with "CFS/ME" appears to have had **only had one hour of rest in the entire week**.

If this illustrative diary is in any way typical of PACE Trial participants, then they do not appear to be unwell at all.

Without any apparent awareness of illogicality on their part, the authors being the next section: "*A very common factor that contributes to the maintenance of CFS/ME is reduced activity and increased rest"*. Anyone who could claim a weekly diary akin to the one the authors have provided as illustrative for a"CFS/ME" patient does not suffer from *"reduced activity"*.

The authors then tell participants: "*It is crucial that the first step of your graded activity programme is stabilising your physical activity….Through this, your body is given time to adapt to the amount of activity it is doing and as a result you're not constantly trying to recover from symptoms"*.

How does this apply to a person who is moderately affected by ME/CFS but doing their utmost to keep going, still less to someone who is so ill that they struggle to bathe and feed themselves? Moreover, the idea that ME/CFS can be stabilised at all is unproven.

On page 52 of the GET Manual for participants the authors set out their view of "*The normal response to exercise"*; whilst true for healthy people, it is is unlikely to apply to sick people and is therefore dangerous misinformation for people with ME/CFS.

Such "normal" responses to exercise are said to include: "*increased breathing rate; increased heart rate; body parts turning red in colour; sweating; increased temperature; 'jelly feeling' especially in arms and legs"*, but none of this takes into account the additional consequences resulting from the documented abnormalities of muscle seen in ME/CFS.

The authors follow up the normal response <u>to</u> exercise with their view of the normal response <u>after</u> exercise, which they assert includes *"manageable stiffness and tiredness"*; this is claimed to be "*a positive sign that the body is adapting and strengthening"*, a misleading and potentially dangerous assertion that does not apply to people with ME/CFS any more than it does to people with motor neurone disease or multiple sclerosis.

The continual reiteration of the phrase "normal response" may teach participants to distrust their own body and to ignore symptoms that may be significant. If participants feel not just stiff and not just tired, but experience flu-like malaise after exercise, are they to interpret <u>that</u> as a "normal response"? How would they know, having been taught to disregard what their body is telling them?

The authors train the therapists to tell participants that "*moderate or intense stiffness do not indicate harm to your body"* (but they might well indicate harm for a person with ME/CFS).

Participants are advised that serious adverse reactions to exercise are rare and the message is that it is safe to keep on with the prescribed exercises.

Next comes a section on the Borg Scale which is a measure of perceived exertion (see the section on the Therapists' GET Manual above), about which the authors state: "*Do not concern yourself with any one factor such as leg pain or shortness of breath, but try to concentrate on your total feeling of exertion"*. This seems to be measuring the unmeasurable, which is the hallmark of Cargo Cult Science (see Section 3 above).

Participants are told that they will be lent a heart rate monitor so that they can measure how hard they are working during their exercises and are instructed on how to use it (it is to be strapped under the shirt and it transmits a signal to a receiver on a strap like a watch strap).

This makes all the more incomprehensible Professor Peter White's decision to abandon the use of actigraphy monitors that are strapped round an ankle and which provide an objective measure of improvement (or otherwise); compared with using a heart rate monitor and the need to keep daily activity diaries, RPE scores, goal sheets, exercise diaries, GET plans, progress sheets and other records, the wearing of an actigraphy monitor for a week at the end of the PACE Trial would not be at all onerous.

Participants are then subjected to more "*positive reinforcement*" and are told that the authors believe that "*muscle soreness"* after unaccustomed exercise *"is a normal response to increased exercise or physical activity, and that it can even be seen as a positive sign that our body is being challenged and is strengthening"*; this is the reiterated personal view of the authors presented as though it were a generally agreed fact but is inappropriate for people with ME/CFS.

More "*positive reinforcement*" follows: "*The good news is that our muscles respond well to techniques that make them feel less tension and more relaxed"* – the authors' explanation for muscle pain in ME/CFS is unproven; the possibility that participants may have underlying physical disease has not been addressed and is clearly not to be contemplated.

Endless admonitions to carry out strengthening exercise follow; (why do them? how often should I do them? where should I start? when should I do them? what should they feel like?) and the inevitable assertion (*"positive reinforcement"*) that participants get stronger with exercise (which again is another unqualified statement that participants will get stronger, not that they might get stronger).

This whole section of the GET Manual for participants is deeply disturbing. It entirely disregards the substantial evidence of muscle pathology in ME/CFS and participants are repeatedly told that they should ignore exercise-induced symptoms in muscle (because they are "normal") by therapists who have been taught to believe that "CFS/ME" is the consequence of deconditioning, which is to deny the significant body of evidence that proves such a belief to be gravely erroneous.

In the section "*Using exercise equipment at home"*, participants are advised that if their graded exercise programme includes a *"treadmill (or a) cross trainer"*, it is their own responsibility to familiarise themselves with the equipment users' manual. What are the correct diagnoses of people who have been included in the MRC PACE Trial? If a participant is able to use such equipment consistently, then they do not have ME/CFS, nor do they have the ME component of "CFS/ME", and it is misleading for the Investigators to claim that they are studying such patients.

Topics such as *"sleep hygiene"* are addressed at length (*"sleep hygiene"* should include a "*wind-down routine"*; establishing *"an optimal sleep pattern"*; calculation of total time asleep on an average night; *"preparing for sleep"*; *"using muscle relaxation"* techniques, including advice on when to use muscle relaxation techniques to help induce sleep, and using a *"relaxation script" --- "you can then allow this feeling to float now towards the muscles of your arms…you may now find that there is more space between your teeth…just notice how simple it can be for your muscles to feel better"*) but information that would help people accurately to understand their symptoms is not mentioned because such biomedical evidence as illustrated in Section 2 above does not feature in the Wessely School's model of "CFS/ME".

Moreover, recent research has compellingly demonstrated that *"activity-related symptom worsening is not caused by worsened sleep"* (Togo F, Natelson BH, Cook DB et al. Med Sci Sports Exerc 2010:42(1):16-22).

In the PACE Trial, the biomedical evidence is denied and disregarded; there is emphasis on *"Motivating yourself"* and participants are given a list of *"ideas that may help you to keep to your programme*" (more "*positive reinforcement"*); these ideas include:

- *"Keep a written plan at all times*
- *"Write down details of your exercise or physical activity achievements*
- *"Keep lists of plans and tick them off once you have done them*
- *"Keep a diary outlining all the things you learn from your GET*
- *"Tell friends and family about your plans and progress*
- *"Reward yourself when you have stuck to your plans, e.g. putting some money aside every time you undertake your plan* (many people with ME/CFS are in receipt of State benefits and are barely able to survive financially, so this "idea" illustrates how out of touch with reality the authors are)
- "*Frequently go over your old plans and exercise sheets and see the progress you have made* (more "*positive reinforcement*")
- *"Become familiar with the GET theory*
- *"Draw a graph of the progress you are making so that you can see your exercise time going up* (yet more *"positive reinforcement*")
- *"Do your activity or exercise with other people*
- *"Become involved in a club or gym…so that you can become committed to your plans".*

The whole flavour of this section appears infantile yet coercive.

Next comes a section on "*Dealing with setbacks"* in which GET participants are told: "*Setbacks are a normal part of getting better"*. This is an irresponsible assertion by the authors because not only does it imply that recovery is expected by reinforcing the message that participants <u>will</u> get better (more *"positive reinforcement"*) when there is no evidence of recovery from ME/CFS, it also untrue because "*setbacks"* (more accurately called a relapse) are <u>not</u> a *"normal part of getting better".*

The authors even augment the misinformation by claiming: "*Therapy usually follows an 'up and down' pattern, but with an overall upwards trend"* (*"positive reinforcement"* again, which ignores the evidence that at least 25% of people with ME/CFS do not improve with any "therapy").

GET participants are told (in bold text in the Manual): *"**The good news: it is normal for setbacks to become less severe, more manageable and last for less time as you get better…the overall trend is usually upwards**".*

This seems to be intended to encourage compliance and is another unqualified assumption stated as fact; moreover it might instil despair into those participants who may not be improving (if, that is, any participants selected for the PACE Trial fall into such a category, since the Investigators anticipated having people on the trial who were walking for 30 minutes each day anyway).

The message about "*setbacks"* is clear: during a relapse, GET participants must "*maintain as much physical activity as you can".* The authors do, however, concede: *"if you are not feeling well due to a CFS/ME setback, then the advice is different"* but they then negate what they themselves have just advised:

"*During a CFS/ME setback, it is understandable that you might wish to rest and reduce the amount of activity you do, because you don't feel well and activity feels much harder than usual. This may even be a time in which you become concerned that the increase in symptoms may be causing you damage.* ***The evidence we have is in fact the opposite: there is no evidence to suggest that an increase in symptoms is causing you harm. It is certainly uncomfortable and unpleasant, but not harmful"*** (this is in bold text in the Manual).

Such advice seems culpable. It is misleading, coercive, and potentially dangerous and above all, it is entirely incorrect. The therapists cannot know that exercise-induced symptoms do not indicate harm because they are not carrying out biomedical testing on participants. Furthermore, the use of the pronoun *"we"* (***"the evidence we have…"***) tells participants that:

"we", the authors, know for certain that symptoms do not equal harm

"we", the authors, are experts

"we", the authors, know your body better than you do.

Any alleged "*evidence*" to which the authors may be referring is likely to be the Wessely School's work and as they use their own Oxford criteria for chronic "fatigue", they may not have been studying people with true ME.

Worse is to come: "*During a setback it is useful to maintain as much physical activity as you can…try to keep to your exercise and activity plan, knowing* (sic) *that in time your body will adjust…Reducing activity should be avoided if at all possible"*.

An international expert advises that in ME/CFS patients, if metabolic demands exceeds cardiac output for even a moment, the result is death (see Section 2 above).

The authors then address "*Writing a setback plan"* which begins with "*positive reinforcement": "… setbacks are a normal part of CFS/ME recovery"*, which is yet another assertion that recovery is possible with GET, even though this is unproven.

The authors provide an example of a setback plan for GET participants which they advise should be in the form of a "note to self" and includes:

- *"Setbacks are a normal part of recovery: it is the overall trend that is important*
- *"I should try to maintain as much physical activity as I can, even though it may feel more difficult than normal*
- ***"I need to remember that there is no evidence to suggest that my symptoms are causing me any harm***
- *"I should try to get back into any activity I have avoided as soon as I can".*

Participants are being taught that they will recover; they must keep exercising and must obey their therapist, which seems very like teaching participants "auto-brainwashing".

The next section of the Manual is entitled: "*Thinking about the future: maintaining positive changes"* and begins by informing participants that: *"This GET programme will equip you with a great deal of knowledge about your condition"*, an untrue assertion if it is supposed to refer to people with ME/CFS – all it does is to force-feed participants with highly biased and opinionated misinformation about a serious neuroimmune disorder of which the authors appear to know lamentably little.

Participants are told about "*Taking on the programme yourself"* and that they should involve *"friends and family"*; they must keep *"written records for yourself…You are encouraged to keep a book to write in, so that you can summarise your GET sessions and keep a log of what you learned at each stage"* and they must think about *"your onward plans and goals".* Participants must also maintain their *"physical capacity"* and they are urged that: *"It is crucially important not to stop exercising after discharge"*.

Once again, the authors reiterate information that many people hold to be misleading: "*exercise has been shown to be a major factor in preventing various diseases and cancers".*

The section on "*Future goals"* discusses "*Where do I go from here?; where do I start?; current goals; new activities; lifestyle changes and diversification; maintaining motivation and direction"*. Participants are provided with *"Notes on using the Future Goals sheet"* which must include:

- "*Goal number: this is the number of the goal and indicates which goal has the highest priority*
- "*Goal: a brief description of the goal*
- *"How to record progress*
- *"Time scale*
- *"How realistic is the goal: this is a score from 0 – 10*
- *"Future goals: breaking down goals into manageable sections".*

Next comes consideration of return to work or finding a new job, including employment and educational schemes.

It is notable that both the CBT and GET participants' Manuals place much emphasis on returning to work, but that the APT participants' Manual does not. In the APT Therapists' Manual, pages 105-109 are a back-to-work hand-out for participants, but the therapist is simply told on page 109: *"This information can be given out to individual participant* (sic) ***as required"*, so it would seem that the issue of returning to work in the APT arm appears to be at the discretion of the therapist and not a central issue as in the CBT and GET arms of the trial.**

As in the CBT participants' Manual, at the end of the GET participants' Manual is a section entitled "*Information for relatives, partners and friends"*. Again, the authors do not even get the name correct: they refer to *"chronic fatigue syndrome (CFS) / myalgic encephalitis (ME)"* and the section is replete with misinformation, for example, one of the causes of "CFS/ME" is stated to be *"Having high personal expectations and driving to do things 'perfectly'*, which is assumption stated as fact.

Relatives, partners and friends are misinformed about *"What keeps CFS/ME going"*, and are told that being "*out of condition"*, *"an irregular bedtime"*, and *"receiving advice from a variety of sources"* all keep *"the CFS/ME"* going, but – inevitably – that GET can *"aid* ***recovery*** *from CFS/ME"* and that GET can *"reverse"* it (an assumption stated as fact). Relatives are encouraged to *"get involved"* and to *"set aside a regular time each week to discuss how they* (the participants) *are getting on. This will give you the opportunity to reinforce their achievements"* (even relatives must use *"positive reinforcement"*).

As with CBT participants, relatives of GET participants are told that *"Setbacks…are a 'blip' in the recovery phase and certainly do not mean that GET has failed"*. It is untrue that setbacks are merely a blip in recovery from ME/CFS. Participants are further told that "*setbacks*" are temporary (*"At these times, it is important to remind the person that setbacks are only temporary"*), an assertion that is untrue because a relapse for many people with ME/CFS can last for months, years or even a lifetime.

If the person has a relapse, relatives are told they must "*Encourage them to read the appropriate sections of the manual in order to get back on track again",* which for a person with true ME could be contra-indicated and therefore is potentially dangerous advice.

Finally, relatives are told: *"As long as a good balance of activity and rest is maintained,* ***then recovery will be sustained****"*. This is an unproven assertion and is the hypothesis supposedly being tested in the MRC PACE Trial.

This entire Manual for GET participants is full of misinformation, misrepresentation, bias, assumption presented as fact, prejudice, and alarming ignorance about ME/CFS. Even though ethics committees are primarily concerned with ethics and not with science, given what is known internationally about ME/CFS, it is incomprehensible how such a document received approval from any ethics committee.

Comments from someone who has undertaken GET

The comments below can be accessed at http://www.foggyfriends.org and they make extremely disturbing reading.

"I know I probably shouldn't be complaining because I have mild-moderate ME and it could be far worse, but things haven't been going great lately.

"The worst bit is having doctors and professionals who write things off. The crunch came today when I went to see my physio who has been part of the PACE trial. We have had a difficult relationship since I started seeing her a while ago as I have struggled to follow her instructions better and how I should tell the whole world about about my ME because I need support. I have chosen not to tell my parents….Yet my physio has had very strong opinions on this choice of mine and won't let the topic drop.

"On a physical level I feel worse now than when I started seeing her. She is putting this down to my 'poor' management of my condition and the fact that I'm allegedly not following her instructions to the letter. I am trying, but my condition fluctuates so much that it is impossible to stick to a consistent routine and I am not pushing myself just for the sake of ticking her boxes. I am trying my best but it doesn't seem to be good enough.

"Today I had three massive lectures about different things. The appointment lasted for over an hour and I was shattered at the end of it. I feel terribly blamed and demoralised by the whole process. She told me I was 'an intelligent woman who knew what I had to do to get better' (since when did IQ equal health!)…She also told me I'm always far too negative and don't recognise how far I've come. Personally I feel I am just honest and realistic about where I am. What is the point in lying? I spend my life putting on a cheerful front to other people and motivating myself with positives, but sometimes I think I need to say what it's really like.

"I feel like all I get are lectures about how I'm failing myself…I even find myself dressing up the truth to make myself look 'better', which for me is a sign that I'm feeling very criticised and belittled.

"I just wanted to cry after the appointment. I have spent today feeling quite low and demoralised. I can't help my state of health and I am not deliberately doing things that set me back….I keep detailed diaries about food intake, time, activity and mood but can't find any patterns, even though I'm told there must be some. There just aren't.

"She has been promising me progress and better health, I just can't find it. Perhaps it's me after all.

"….She tells me lots of success stories about other patients who have been through the GET programme and are now fully functioning. She tells me I can get there too…She is so positive about this that she isn't at all tuned in to my needs and current state. I also think she's too quick to look for causes of my setbacks when sometimes it's just the natural fluctuation of my condition. The lectures I get are because she thinks she's motivating and helping me, whereas I just feel told off and criticised. Who wouldn't, when they are just told 'You should do this; you shouldn't do that; you need to be stricter with yourself or you won't improve; you've got to get better at x,y and z; you've got to believe in this; you have to work harder at it; I don't think you really believe in this and that's why it's not working'?

"…I was told today that my physio doesn't think she can help me any more as she's taught me all she can so I'm going to have a telephone review in the New Year – and then be discharged, I guess.

"…Re the PACE Trial…I just found out who's involved and it says: 'The PACE Trial is to be designed and managed by Professor Simon Wessely; that Dr Peter White, Michael Sharpe and Trudie Chalder will be centre leaders. So both Wessely and White are involved. As for Chalders (sic)*, her book about 'Overcoming CFS' is not even worth reading.*

"…I've spent today wondering if I really am too negative about my health…However, I'm just telling it like it is and it's not as if I go around constantly moaning about it. In fact it's the opposite, I usually hide it away and cope by myself.

"I do feel under pressure to lie about my progress…I suppose she sees her programme as a neat formula: 'If you do x and y then that equals z', so if it doesn't work for me then I must be at fault.

"…I am feeling like a massive emotional burden has been lifted off me today because I have formally withdrawn from my GET programme…I just cannot go through another session with that physio, even if it's just by telephone.

"…I am not clinically depressed….I wonder what people who are depressed would feel like….It is not acceptable for patients to feel belittled, criticised, patronised and tearful after a GET session.

Having made a complaint, the diarist records: "*The service lead has also withdrawn me from the self-management group. She says it's a waste of my time and if she had thought it was right for me then she would have referred me there herself when she first assessed me. She said she cannot see it being of any benefit to me…She said if she was in my shoes then she wouldn't want to do it.*

"…the service lead said that GET has a one in three success rate and that I clearly fell into the two people that don't respond to it. She said it was not my fault that it didn't work".

These extracts from the diary of a GET participant reveal how mistaken it is for the authors of the PACE Trial Manuals to focus on *"unhelpful thinking patterns"* and on *"thinking errors".*

Furthermore, the extracts reveal many breaches by the physiotherapist of the NICE GET treatment protocol set out in the 2007 Guideline (CG53) and people are wondering if all the therapists in the PACE Trial took the same approach. The answer is that the approach is "manualised", so it is likely that the same approach has been used with other people.

Quotations from the Therapists' Manual on APT

Of all the PACE Trial Manuals, this 183 page Manual seems to be the most poorly-conceived and ill-written. In his reply to comments about the published (abridged) Trial Protocol, Professor Peter White stated about the APT Manuals: *"The manuals were developed in conjunction with and fully approved by the patient charities Action for ME and Westcare (before they merged)"* (http://www.biomedcentral.com/1471-2377/7/6/comments).

The Investigators claim that APT has been used in response to patient feedback and support from various groups, but APT is not "pacing"; there is no description of APT in the public domain, so the claim that it was included because patients find it helpful is difficult to understand (Co-Cure RES: 4th February 2010).

The PACE Trial Investigators' unfavourable views about pacing were already known. In 2002, the same year that Peter White applied to the MRC for funding for the PACE Trial, commenting on the Chief Medical Officer's Working Group Report on CFS/ME and acknowledging the input from Professor Michael Sharpe, he wrote about pacing: *"Some clinicians could not agree to recommend 'pacing' on the basis of patient group experience alone, without any evidence of efficacy….The English report's recommendation omitted any suggestion that CBT and GET should be more readily available; something that would have been helpful since the unavailability of these treatments is the real issue in this country…These recommendations were obfuscated by equally promoting 'pacing', in spite of the lack of research evidence for its efficacy…**The one clear difference between pacing and the more active CBT and GET is that activity levels are limited by symptoms in pacing….The theoretical risk of pacing is that the patient remains trapped by their symptoms in the envelope of ill-health**"* (Editorial: Postgrad Med J. 2002:78:445-446).

The published (abridged) Trial Protocol states about pacing that it: ***"may reduce symptoms, but at the expense of not reducing disability"*** (BMC Neurology 2007: http://www.biomedcentral.com/1471-2377/7/6). The Therapists' Manuals, however, state that all the interventions used in the PACE Trial may be considered forms of pacing -- as mentioned above, the "Summary of Therapies" in the Manuals for Therapists and in the SSMC Manual describes APT as "*simple, non-incremental pacing*"; CBT as "*complex incremental pacing*", and GET as "*simple incremental pacing*". Furthermore, the Full Protocol (final version) states: "*All the participating clinicians regard all the four treatments as potentially effective*", which contradicts Professor White's own views about pacing.

The Minutes of the Trial Steering Group meeting held on 27th September 2004 record that Professor Jenny Butler (an occupational therapist) *"expressed concern that the APT manual appeared to be considerably smaller than those for CBT and GET. Recommendations including copying the format of the GET manual for information on engaging the patient, the initial assessment and troubleshooting such as 'what to do if your therapist is on holiday'* (sic). *It was stated that APT should have equal face validity to the other therapies and because this was a new treatment and one advocated by patient groups, it was important to make this treatment of equal quality".* Action 31 in the Minutes records: *"Professor Sharpe to lead Diane Cox in making the recommended alterations to the APT manual".*

The authors of the APT Therapists' Manual obviously listened to Professor Butler; they increased its size by the use of:

- repetition
- repetition of the repetition (using many almost identical quotes from an AfME survey)
- what appears to be obvious "padding" by using superfluous explanations of elementary concepts
- extraordinarily large font sizes
- pages containing only one or two sentences
- large diagrams as apparent space fillers.

By trying to turn what is common-sense (ie. the avoidance of over-exertion) into a "therapy" (ie. APT) and by providing a "Manual" for this "therapy" (a Manual which amounts to little more than a collection of

anecdotes taken from AfME surveys), in their "*Models of Treatment"* the authors refer to the literature on pain in an attempt to make it sound as if there is an established "scientific" explanation that underpins "pacing" (ie. not just patients' preference).

This has been shown not to be the case: "*It is evident from this review that 'pacing', while a widely employed term, lacks consensus of defintion and a demonstrable evidence-base"* (Gill JR et al; Eur J Pain 2009:13(2):214-216).

It is a matter of record that one of the authors of the Manual (Professor Michael Sharpe) does not believe in pacing, so it is unclear what he contributed to a Manual on a subject in which he does not believe; equally, acknowledgement is made to Peter White for his invaluable contribution but, given his known antipathy to pacing, it is difficult to understand what his invaluable contribution could have been.

As with other Manuals, this Manual has coloured pages: pink sheets divide it into the three phases of "*treatment"* and yellow sheets are the sessions plans and content for each of the 15 sessions of *"treatment"*.

The authors advise the therapists that *"the space between the list of handouts is an indication of which might be used during the session and those that the participant will use at home"*, which seems to be little other than an attempt to increase the size of the Manual.

There is the inevitable overlap with the other Manuals for Therapists, for example, APT therapists are told that CFS, PVFS and ME are to be considered as "CFS/ME"; that the essence of SSMC is good quality medical care, and that APT is widely used and is advocated for patients with fatigue. The Investigators' "theoretical model" is described, as is the definition of CBT and GET used in the PACE Trial.

Page 18 of the APT Therapists' Manual is identical to page 28 of the CBT Therapists' Manual, but with one notable difference: APT does not *"Aim for an improvement in function to occur"*.

Therapists – who are occupational therapists -- are told that all sessions will be taped and that "*Relaxation sessions may also be taped*".

It is notable that in his 2006 Comments on Chapter 6 (page 301) of the NICE draft Guideline, (ie. during the lifetime of the PACE Trial), Professor Peter White stated his views about relaxation: "*…**this technique has often been used as the main component of ineffective comparison treatment arms in several RCTS**….**Why, therefore, is an ineffective therapy included? We suggest this is omitted…."*.

It may be wondered why Professor White had by then received millions of pounds sterling to carry out an MRC clinical trial that includes what he himself asserts is "*an ineffective therapy"*. The APT Therapists' Manual (to which Professor White made an invaluable contribution), however, states: "*Pacing therefore involves practising relaxation to achieve proper rest…. Homework: Planned relaxation and activity set at an achievable level, practised regularly and consistently…".*

APT Therapists are told: *"The aim is to provide the best conditions for natural recovery to occur. A lessening of activity-related symptoms is regarded as evidence of recovery which may permit an increase in activity"* and that *"The pacing therapy used in this trial is based on that reported as useful by people with CFS/ME and collated by the patient organisation Action for ME (AfME 2002, 2003)".*

The key words appear to be *"based on"* the pacing reported as useful by people with "CFS/ME" because it appears that "APT" is different from the pacing reported as useful: APT is "adaptive" pacing, which is substantially different from "pacing".

As noted above in the introduction to Section 4 of this Report: "*Activity is therefore <u>planned</u>"*, which indicates a structured activity/rest regime, and the APT Therapists' Manual lists requirements for APT including "*plan <u>set activity</u> 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 "doing what you can when you can".

To reiterate: the PACE Trial version of "pacing" (APT) requires homework and practice and includes planned relaxation and activity, practised regularly and consistently (ie. effectively to a timetable) and the use of daily diaries in which participants must analyse their own activities. Participants must undertake breathing exercises and APT involves its own targets and methods. Its aim is that the participants do not remain at a fixed activity level.

The "Theoretical Model" of APT is "*The concept of fixed limits"* and this is explained: *"The basic underlying concept of adaptive pacing is that CFS/ME is an organic disease that the person can adapt to but cannot change"*.

This is clarified for the therapists: "*Because people with CFS/ME are likely to be particularly sensitive to, and fearful of, a perceived over-emphasis on psychological factors, a physical model of disease that limits energy is emphasised and used throughout treatment"*.

Does this mean that the PIs acknowledge "CFS/ME" to be an organic disease in one arm of the PACE Trial but not in two other arms of the same trial, or are APT participants being misled about the PIs beliefs, (because in the other Manuals, a "*physical model of disease"* equates with deconditioning)?

It is notable that, unlike the Therapists' Manuals for CBT and GET, the APT Therapists' Manual states: "*Symptoms are regarded as warning signs to be 'listened to'. It is assumed that the symptoms reflect a pathological disturbance….good pacing will maximize the chance of natural recovery…Activity is therefore planned so as to balance activity and rest"*.

On page 21 of this Manual, the authors state: "*There have been a number of supporters of adaptive pacing therapy for chronic fatigue syndrome"* (once again, there is no mention of "CFS/**ME**"), but there appears to be confusion between "pacing" and "adaptive pacing therapy" because APT involves <u>setting goals for increasing activity</u>: "*The essence of pacing is that the person with CFS/ME uses self-management of their level of activity…The aim is to prevent sufferers entering a vicious cycle of over activity and setbacks, **whilst assisting them to set realistic goals for increasing their activity when appropriate**"* (which is the first mention in the Manual of *"increasing activity"* as part of "pacing").

The Manual continues: "*The main key to effectively managing symptoms is limiting the amount of energy expenditure. Examples of how patients describe this are: 'stopping what you are doing when the warning of fatigue starts' (and) 'knowing how much to do before resting…' (188 & 225 AfME 2003)"*.

It is notable that the PACE Trial Investigators are willing to accept the AfME survey results on pacing as reliable but dismiss the AfME survey results on GET.

The authors then state: "*Too much activity or too much rest can each be unhelpful (AfME 2002)"*. That "too much rest can be unhelpful" comes from "Guidance on the management of CFS/ME", an eight page document produced by AfME in 2002 "*to assist GPs in the assessment and management of patients with CFS/ME",* but it should be compared with AfME's major report of 2001 (Severely Neglected: M.E. in the UK), in which 91% found rest (including bedrest) to be helpful; 8% found no change, and only 1% found rest made them worse, so for the authors of the APT Therapists' Manual to quote the AfME 2002 document seems disingenuous.

On page 23 of the APT Manual for Therapists, they are informed that: *"…the person with CFS/ME alternates from relative symptom-free rest to activity-induced symptoms"*; this again, is assumption presented as fact, because people with ME/CFS may <u>not</u> be *"relatively symptom-free at rest"*. People with true ME may be in constant pain when at rest; they may experience nausea, dizziness, sweating, shivering, breathlessness,

cardiac arrhythmia, shaking, muscle spasms, leaking blood vessels resulting in spontaneous bleeds, vascular spasms, and intense malaise ("feeling terrible") even at rest.

Therapists are told that participants should ensure that activities are interspersed with periods of proper rest and that *"Another (way) that may enable the person with limited energy to achieve more is to alternative* (sic) *activities"* (one can only wonder if anyone proof-read this Manual).

Therapists are advised that: *"As natural recovery occurs the person with CFS/ME may find that they feel able to increase activity. When such recovery occurs the person may wish to establish a new baseline. Activity…(is) built up as tolerance increases"*. Not only is there no guarantee that natural recovery will occur, neither is there any evidence that "tolerance" will increase in patients with ME/CFS (who may be struggling to maintain enough energy necessary for basic survival).

The Manual then informs APT Therapists about *"Therapists Preparation and tools"* and about *"General Adherence to Protocol"*; cancellations or failure to attend must be *"rearranged within 5 working days if possible"*; *"Telephone contact between sessions …is not banned but should be discouraged"*; "*if a participant no longer wants to participate in the trial…the centre leader…should be informed on the same day…"*; *"each session should be audio/or video taped"*.

Therapists are instructed in the *"Knowledge and skills required"*, which include *"empathy, warmth, rapport, supportive encouragement, interactive communication, active engagement between therapist and participant, problem solving, involvement of family members, and liaison with employers, other health professionals and other outside agencies"*; therapists are instructed that it is important they convey to participants their "*belief in the reality of their symptoms"* and therapists are told they are required to *"demonstrate a sound knowledge of CFS/ME as participants will generally be well-informed about their illness"* (many occupational therapists, including those working in the "CFS" Centres from which PACE Trial participants were referred, are known to believe that ME/CFS is a behavioural disorder -- see RiME NHS Clinics Folder at www.erythos.com/RiME).

The authors then re-instruct the APT Therapists that: *"People with CFS/ME are often sensitive to the over-emphasis of psychological factors"*, a curious statement, given that the APT therapists are supposed to be working on the assumption that "CFS/ME" is an "*organic disease"*.

Notwithstanding, the CBT Therapists' Manual cautions: "*In order to maintain participants engagement throughout treatment, it is important that you continue to use an integrative model and avoid promoting a rigidly dichotomous view of physical and psychological illness"*.

APT Therapists are informed that participants *"may find that their symptoms initially worsen when they start their APT programme"*, but if true pacing is used (which APT is not), symptoms are unlikely to worsen when patients pace themselves.

On page 31 of the Manual, APT Therapists are told: "*Collaboration is an essential skill when working with people with CFS/ME"*: (surely collaboration is essential with all patients, whatever disorder they may be suffering from?) and that: "*It is essential that you demonstrate positive reinforcement when you work with people with CFS/ME. Often they will be very good at pointing out what they haven't achieved"*.

This seems to convey the message that "CFS/ME" patients are somehow different and even psychologically aberrant; indeed, the PACE Trial Manuals disparagingly refer to *"these people"* as though participants are a different and difficult species. Perhaps this explains why APT Therapists are advised that: "*Another useful communication technique to assist in problem solving is the 'broken record' technique – where you repeat the …statement frequently within a session to emphasise a… point"*.

The Manual continues (page 33): "*What are the available solutions? Brainstorm tried and tested solutions…Use your imagination and be creative, even the most outlandish possibilities are worth considering"*. How *"outlandish"*

are the "*solutions*" that are to be applied to sick people suffering from ME/CFS, and who monitors the appropriate degree of *"outlandish"* that may be perpetrated upon *"these people"*?

Therapists are informed that they must *"Practice the strategy"* and must use *"role play"*. How effective *"role play"* might be in an MRC clinical trial that is allegedly aiming to help people with "CFS/ME" recover from their illness is not clarified, but it is unlikely that "*role play"* would feature in an MRC Clinical Trial to help people with Parkinson's Disease or multiple sclerosis or motor neurone disease.

In the section "*How to Structure Treatment Sessions"*, the authors deem it necessary to remind the therapists to *"Read your previous session notes before the participant comes into the session"* and to *"Book the next appointment"*.

Therapists are also reminded that *"Every session should contain the following: A review of homework and the participants diaries; Review of the APT model; Time to check out the participant's understanding of any new techniques you may have introduced during the previous session….(and) Time to plan homework"*.

The next section of the Manual (page 36) purports to address: "*Discussing what is required of the Participant"*, which includes:

- *"To complete all records, e.g. daily diaries*
- *To commit to prioritising treatment over the coming months* ("treatment" is not specified)
- *To contact you as soon as possible if they are not going to be able to attend an appointment*
- *To keep you informed of any changes in medication*
- *To participate in setting an agenda each session so that all of their needs and requirements are met*
- *To feel able to tell you if they are not clear on any aspect of the treatment*
- *To attend appointments on time"*.

This is followed by: "*Helping participants to become their own therapist: The overall aim of therapy is to help people learn to become their own therapist by helping them to become an expert in managing their own problems"*.

This was to be achieved by:

- *"Giving clear explanations about the APT model*
- *Repeating the rationale for APT to reinforce the model and to increase the participant's level of understanding*
- *Checking the participant's understanding when discussing new strategies*
- *Encouraging participants to evaluate the progress that they have made since the last session*
- *Agree set-back plans before participants are discharged…so that they feel confident in managing an increase in symptoms"* (an anticipated increase in symptoms seems to be more evidence that APT is not "pacing" as generally understood).

The APT Therapist is then advised about *"Involving a relative or friend in a therapy session: Participants may find it helpful to have a partner, relative or friend to attend a session with them. It can provide them with support and encouragement, particularly when they are experiencing difficulties with their APT programme"* (which again indicates that APT is not "pacing").

The Manual continues: "*For participants who do not want to have a relative or friend attend one or two sessions: Ask the participant whether they would like their relative or friend to attend an appointment with them"*.

Unaccepting of the fact that a participant may not <u>want</u> a relative or friend to be present, the therapist must: *"Ask the participant to suggest that the person reads the section at the back of the participants manual for partners, relatives and friends"* (because there must always be "*positive reinforcement"* – or "brainwashing" --throughout the PACE Trial and this must take place not just during attendance sessions but also at home).

If a participant asks the therapist not to record the session, the therapist is instructed to: *"ask them the reason why…(and) try to get permission to switch on again as soon as possible".*

On page 40 of the Manual, therapists are informed that *"It is perhaps inevitable that therapists will find that they have mistakenly given a cognitive interpretation, or encouraged a form of exercise, especially in the first few months as they are learning"* (why would it be "*inevitable"* when APT is antithetical to the CBT/GET model?).

If participants ask "difficult" questions, such as "*expressing doubt over APT as a result of reading or press"*, the therapist must not ask the participant what they think (this would be CBT), but can suggest they *"discuss with the clinic doctor".* If a participant has been *"advised not to continue with APT by an outside influence"*, the therapist must *"Contact centre leader and discuss with APT lead".*

The next section of the Manual addresses *"Frequently Asked Questions, comments and issues". There are a number of questions that participants may ask during treatment. Below are a number of those potential questions and the possible responses you could consider to bring the person back to the APT model"* (it is unclear if this is just badly written or if it amounts to coercion to keep the participant engaged in the trial at all costs). Some illustrations include the following:

"Is this a cure?

- *Be honest, the answer is no"* (APT has never been trialled before, so how do the authors know that it is not a cure? CBT/GET participants are told that they can *"overcome"* their "CFS/ME" but the APT participants are told that they cannot; this is unacceptable in an MRC clinical trial because it would inevitably have a nocebo effect – nocebo being the antonym of placebo)
- *Aim of APT is to enable/facilitate a natural recovery response*
- *Aids natural recovery* (surely this is the same as the aim directly above?)
- *Recovery is achieved by balancing rest and activity* (bullet point 1 states that APT is not a cure, whilst the final bullet point says that with APT, **recovery is achieved** by balancing rest and activity).

"How do I deal with a set-back?

- *Adjust any programme…rather than increase your activity*
- *Main advice = rest* (it is important to recall that the Oxford [ie. the trial entry] criteria allow participants with psychiatric disorders such as depression to be enrolled in the PACE Trial; if depressed people are told to rest, they may become even more depressed and the result will be that APT appears ineffective, an outcome which many people believe would suit the Principal Investigators, whose views on pacing are known to be unfavourable)
- *Make realistic goals*
- *Listen to your body*
- *Re-consider balance….needs versus wants";* participants are to be advised to *"re-read the Adaptive pacing model of CFS/ME".*

"What is an exacerbation of symptoms?

- *When symptoms have increased beyond your normal range*
- *Symptoms level stops you doing your baseline".*

"What do I do on a bad day?

- *Rest, relax, sleep*
- *Consider reasons*
- *Re-assess baseline.*

"My illness is physical?

- *Yes"* (participants with the same disorder but in different arms of the same MRC clinical trial are considered not to have a "physical" illness).

The section beginning on page 49 of the Manual (*"Implementation of therapy"*) repeats what has appeared earlier in the Manual (for example: *"Because people with CFS/ME are likely to be particularly sensitive to, and fearful of, a perceived over-emphasis on psychological factors, a physical model of disease…is emphasised and used throughout treatment"*).

There were to be fourteen treatment sessions, the first of 90 minutes, the rest of 50 minutes, over a period of five months; the first four sessions were to be weekly and subsequent sessions were to be at two weekly intervals.

Session 1 is entitled *"Information Gathering and Treatment Rationale"* and the therapist must ascertain the participant's "*thoughts as to what caused CFS"*. Later in the same session, the therapist must ask: "*What do you think is causing your current difficulties"* (but the "APT model" assumes "CFS/ME" is an organic disease, so what else would be causing the participant's *"current difficulties"*, and why describe an organic disease as a *"current difficulty"*? This seems to indicate that the authors of the Manual do not actually believe that ME/CFS is an organic disease).

The next question that the therapist must ask is: "*Do you have any specific plans to resolve your current difficulties?"* – would this question be asked of people with multiple sclerosis?

Next, the participant is to be asked: "*Have you come here today with any particular… goals….?"* (the goal of people with ME/CFS is to get better and to resume their premorbid life-style).

Session 2 is entitled: "*Review pacing model and individualise to the person with CFS/ME"* and the participant must *"Continue self-monitoring: Activities Must do/Like to do"*. It continues: "*An example of a patients (AfME 2003, 80) description is: 'Accepting that recovery will come when you stop trying to be a superwoman….With progress I have increased the activities undertaken"* – this is inconsistent: the participant has been told that APT is not a cure, but here the participant is being told that recovery will come if she stops trying to be a "superwoman". The clear implication is that ME/CFS symptoms are caused by a hectic, exhausting lifestyle and not by an organic disease.

Session 3 is entitled "*Planning how to implement pacing"*. An analogy is to be used: "*I use the image of a bank account. I always have to be careful not to use the overdraft. I have to rest when I still have some money in my account"*.

Session 4 is entitled "*Equilibrium between activity and symptoms"*; quoting AfME 2003, 87, this is said to be: "*Aiming as far as possible to ensure that each day has around same level of activity. It works!"* – but the participant has already been told that the aim of pacing is to assist them to *"set realistic goals for **increasing** their activity"*.

Session 5 is entitled "*Priorities and Standards of Activity"*; participants are to be instructed: "*Rest/relaxation means no TV, reading, conversation, music"*. Homework must include "*Prioritising what you would need/like to do and allocating energy to do it"*.

Session 6 is entitled "*Body Mechanisms and Activity Analysis"*; the"*rationale for treatment is re-explained as necessary"*; the therapist must *"Introduce Activity Analysis"* and must also introduce *"Energy Conservation as a Concept"*. Therapists are told that, according to AfME 2003, 253, *"A person's explanation of activity analysis"* is *"Pacing means looking at my daily activities and breaking them down into achievable chunks"*.

Sessions 7 – 12 are entitled "*Review model and treatment aims"*.

In session 7, there must be *"Activity Analysis, alternating activities & activity modification…pacing means… trying not to push too hard"*.

Session 8 is entitled "*Pressure from self and others to deviate from pacing"* and includes "*Plan your time; Keep to your limits; Set appropriate targets; Alternate activity and rest; Modify your activity".*

Session 9 is entitled "*Anticipating exacerbation's"* (sic) which includes:

- *"Discuss and revisit balance*
- *Revisit must do/want to do activities*
- *Revisit priorities and re-set limits and priorities*
- *Discuss 'listening to your body'*
- *Re-set energy levels and weekly plan*
- *Practice rest/relaxation techniques as required"*

Session 10 is entitled "*Increasing as Able".*

*" ….As natural recovery occurs the person may find that they can increase activity …**When such recovery occurs** the person may establish a new baseline…However appropriate aims and priorities can be set and then activity built up as tolerance increases".* Homework must include "*Balancing activity"; "Breaking down large tasks into small chunks"* and "*Importance of monitoring….keep brief notes to work out what you can and can't do to maintain progress (AfME 2003, 354)".*

Session 11 is entitled "*Baseline Review"* and is to include:

- *"Review baseline*
- *Review balance between*
  - *-- activity and rest/relaxation*
  - *-- physical and mental tasks*
  - *-- work and leisure*
  - *-- needs and wants.*

Handout:

- *Baseline sheet*
- *Weekly schedule*
- *Daily schedule*
- *Energy grid".*

Homework must include *"Planned relaxation and activity set at an achievable level, practised regularly and consistently. Completion of homework diaries and weekly and daily schedules".*

Session 12 is entitled "*Rest, relaxation and sleep pattern review. …Homework… means having a calendar & putting all engagements on it making sure they are well spaced out then I can arrange what I have to do around house/garden/ shopping to fit in again well spaced* (sic) *(AfME 2003, 93)".*

Session 13 is entitled *"Questions and consolidation"* and states: "*The rationale for treatment is reviewed and the person's successes and setbacks in implementing pacing discussed".* Homework is to include "*A written summary of the treatment is produced as homework. In particular, learning achieved"* (sic).

Session 14 is entitled "*The way forward".* The only entry states: "*Review learning".* There are *"Handouts"* which include "*APT model diagram* (if at session 14 the participant did not know what the "APT model" is allegedly about, then the therapist has failed in the task); "*Target Review*" and "*Baseline Sheet".*

"Paperwork to complete after session" includes "*The Clinical Global Impression (CGI) is also completed by the therapist after this session".*

Three months after the end of session 14 there is to be a "*Follow up"* to:

"Review programme:

- *Daily plans*
- *Weekly plans*
- *Activity analysis and modification*
- *Energy conservation and regulation*
- *Use of rest and relaxation*
- *Sleep pattern*
- *Aims, targets and priorities*
- *Balancing life".*

The remaining pages of the APT Therapists' Manual are Appendices 1 – 4.

Appendix 1 consists of "*Diagnostic criteria"* and includes photocopies of the Fukuda et al 1994 CDC criteria; the 1991 Oxford criteria, and appendix II to the *"CFS/ME Working group report 2001" – existing diagnostic criteria (adults)"*.

Appendix 2 consists of *"Tools for recording sessions and information"* and includes "*Record of attendance for APT"; "PACE Trial Session Record"; "Unplanned Telephone Call record"*, and "*Reflective Review of Session"*.

Appendix 3 consists of "*Therapist resources"* and includes "*Relaxation 1 (Warmth and Light); Relaxation 2 (At Peace with Pain)"; "Activity Analysis Overview: Physical; Sensory; Perceptual; Cognitive* (but cognitions were to be excluded from the APT model)*; Emotional; Social; Cultural; Environment* (sic)*".* The therapist is advised: "*You may wish to add your own local contact resources here. Suggested contacts/information sources: Citizens Advice Bureau* (exactly how much accurate information the CAB might hold about ME/CFS is not clarified); *Employment and educational schemes such as Job Centre Plus, Learn Direct etc; Welfare Rights; Locality issues; PACE Trial integrity Rating Scale".* Pages 105-111 are the same as pages 95-100 of the CBT Participants' Manual, though the sections appear in a different order.

Appendix 4 consists of "*Participant handouts"*; pages 114-183 appear to be the APT Participants' Manual.

A number of senior clinicians, medical scientists, statisticians and health analysts who are conversant with this Manual have been derisory about it, variously describing it as "asinine"; "puerile"; as having "nothing to do with medical science", as "a disgraceful waste of money" and as "bringing disrepute upon the MRC", amongst other comments.

Quotations from the Participants' APT Manual

This 72 page Manual competes with the APT Therapists' Manual for being the most banal of all the Manuals; it contains the same misleading information as in other Manuals, for example, it states that doctors are unsure if ME, CFS and PVFS are the same disorder, so they decided to refer to it as "CFS/ME".

It is a remarkably sparse "Manual"; the repetition and lack of content must surely have left participants thinking that this was no therapy at all.

Not only is it lacking in content but the Manual is unjustifiably patronising. It includes childish and inane cartoons of a piggy-bank, a battery, a set of weighing scales, a picture of a dollar coin cut to look like a pie chart, and three envelopes, each of which fills most of a page. The same cryptic diagram which fails to communicate anything meaningful about APT appears twice, once on page 9 and again on page 69.

Page 5 of this Manual explains APT to participants: "*The underlying idea is that if people with CFS/ME use their energy wisely, their limited energy will increase gradually…The essence of pacing is that the person with CFS/ME uses self-management of their level of activity in order to avoid exacerbations of symptoms".*

The Manual quotes from the 2002 Chief Medical Officer's Working Group Report and, as with the APT Therapists' Manual, relies on the Action for ME (2002) document that purportedly summarised that Report, for example: "*Too much activity or too much rest can each be unhelpful".* As mentioned in the section on the APT Therapists' Manual above, only 1% of people with ME/CFS found that rest was unhelpful.

In the section *"Important strategies used in pacing",* these are listed as:

"Establishing a baseline:

"…the person with CFS/ME alternates from relative symptom-free rest to activity-induced symptoms" (once again, this is an assumption stated as fact, because people with true ME may not be symptom-free at rest; as noted in the comments on the APT Therapists' Manual, symptoms experienced even at rest are likely to include pain, nausea, dizziness, sweating, shivering, breathlessness, cardiac arrhythmia, shaking, muscle spasms, vascular spasms, and intense malaise ["feeling terrible"] even at rest).

"*Dealing with pressures to deviate from pacing:*

"…You will be encouraged to find ways to keep within limits.

"Anticipating exacerbations:

"…You will be encouraged …to set limits rather than wait until severe symptom exacerbation has occurred.

"Proper rest:

"…Pacing involves practising relaxation to achieve proper rest.

"Alternating activities:

"…It is noted that people with CFS/ME may become fatigued because they have persisted too long with an activity. One way to avoid this is to limit activity…".

The emphasis is on "fatigue"; other cardinal symptoms of ME/CFS are ignored.

Participants were to be given a handout sheet on which to record their *"Fatigue Level"* (again, no mention is made of other symptoms). The blank record sheet is photocopied in a full page of the Manual, which seems nothing more than a space-filler.

Then comes a section entitled *"Participant Handout: Bust and Boom Peaks and Troughs"*, which states:

"People often describe a see-saw effect to their symptoms.

"This can be on a daily, weekly and monthly basis" (The configuration of the page is noticeably extended and seems designed to fill the space).

"The process is,

- *When feeling better do more in an attempt to catch up*
- *When feeling worse, symptoms increase* (surely this is the wrong order – symptoms increase and the patient feels worse; moreover these are isomorphic)
- *Do less, 'rest'*
- *Feel better and so on.*

"This can be described as an over activity/under activity cycle".

"The diagram below shows this" (the diagram is missing, suggesting poor editorial control).

Page 13 of the participants' Manual states: *"Participant Handout: General Principles of Adapted* (sic) *Pacing"*

"Summary:

- *Listen to your body*
- *Alternating rest and activity*
- *Doing one thing at a time*
- *Choosing low energy activities*
- *Using energy saving devices*
- *The 70% rule* (described earlier in the Manual as *"never going beyond 70% of a sufferer's perceived energy limit")*
- *Achieving balance*

There is virtually no substantive content, and many pages are mostly empty.

Page 14 of the Manual contains only 21 words, all in large font:

"ACTIVITY BASELINE. A comfortable level of activity that can be managed on a regular basis, without experiencing an increase in symptoms".

Page 15 states: *"Participant Handout. DATE: NAME: Baseline Sheet: A baseline of activity is a comfortable level of activity that you can manage on a regular basis, without experiencing an increase in symptoms. What would be your own baseline at present?"* (most people with ME/CFS are unable to establish a baseline because of the fluctuating nature of the symptoms, and this is a defining characteristic of the disease).

Page 16 states: *"Participant Handout List of Activities. Date…….Name……."* and consists of a blank record in two columns, one side headed *"Must do activities"* and the other side headed *"Would like to do activities"*.

How does this constitute a "therapy"?

Page 18 asks: *"What is Recreation?"*. It continues: *"Recreational activities are what you may have previously described as relaxation…for example going to the pub after a busy day at work to unwind, watching the TV, and gardening….Recreational activities…will, in time as your body allows, need to be reintroduced as part of your programme of rest and activity".*

"What is rest? Rest is a way to bank and restore energy".

"What is Stress? Stress can be anything that disturbs your status quo. This can be mental or physical".

"What are stressful events? A stressful event can be anything that you perceive as threatening, change in your life or disturbing emotions…The list is endless".

"What reaction can stress cause? ….If stress continues for a long time, the body may be unable to maintain its balance and may 'break down'. This may take the form of chronic conditions….".

"What role can stress play in CFS/ME? Stress may be involved in two ways.

"1. It may help to cause or trigger the illness….

"2. Once the syndrome is established stress may be the cause of some of the symptoms. Certain complaints such as nervousness, muscle tension….palpitations and sweating – are all symptoms common in CFS/ME".

"What can I do about stress? There are two things you can do;

"1. You can try to identify and remove the sources of stress in your life

"2.You can help your body to maintain its balance and prevent symptoms of stress. This can be done in various ways. These include learning…the importance of effective relaxation through the use of techniques such as…relaxation"(sic).

Next comes a page entitled "*Participant Handout Managing your Sleep"*, which states: "*Drinking too much coffee and tea may also cause difficulty with sleep for some people with CFS/ME….As you rebalance your activity and rest, you may notice an improvement in your sleep pattern".*

Page 47 is entitled *"Participant Handout Ergonomics and Activity Stations".* Advice given includes: "*Some tools and technology can increase independence such as scooters, walking sticks and disabled parking permits"* (this differs from Peter White's 2006 submission to NICE, where he objected to the provision of such aids for people with "CFS/ME" – http://tinyurl.com/2fpjxc).

Page 49 of the Manual is entitled *"Participant Handout Activity Analysis. Activity analysis is taking an activity and breaking it down into its component parts….Whenever possible, simplify the activity…For example throw laundry downstairs in a bag or pillowcase rather than carrying it".*

On page 50, participants are advised: "*Don't forget to bank and budget for energy:*

"Banking Energy:

- *Activity Analysis*
- *Activity Modification*
- *Rest and Relaxation*
- *Balancing work, rest and play*

"Budgeting Energy:

- *Evaluating priorities*
- *Evaluating standards*
- *Planning your day".*

Page 51 is a blank record sheet for *"Energy requirement*".

Page 52 is a blank record sheet for *"Activity Station Analysis Sheet".*

Page 53 is a blank record sheet for *"Activity Modification Worksheet".*

Pages 54–58 are descriptions of Ergonomics (described as *"the study of 'the relationship between workers and their environment' ").*

Page 59 is about *"Work Simplification". "What does Work Simplification mean?".* Participants are advised that it means: *"Preparation; Performance of the task itself; Clean-up/putting things away".* Participants are then told about *"Basic Principles of Work Simplification".*

Page 61 (another Participant Handout) summarises *"Adaptive Pacing Therapy Aims and Methods"*; these are listed as:

"*Establish a baseline*
"Introduce proper rest and relaxation
"Save and budget energy
"Improve sleep
"Live within your limits/baseline activity
"Use ergonomic technique
"Devise a way to recognise energy expansion…Think of the last time that you had a 'better' period of functioning. How did you know you had improved?".

Next comes a section on how to deal with *"Pressure from Self and Others to Deviate from Adapted* (sic) *Pacing"*, which consists of quotations from the AfME (2003) Report. It is notable that no mention is made of the fact that the main pressure to deviate from pacing (ie. resting as necessary) comes from the Wessely School, which over the last two decades has influenced the attitudes of GPs, as well as press reporting of the disease, which is known to have influenced attitudes of friends and family.

On page 64 of the Manual the participant is advised that *"Problem solving will not be new to you; it is something we all do on a daily basis in relation to the tasks we need to perform".* Participants must:

"*Identify the problem.*

"What are the available solutions? (as in the APT Therapists' Manual, participants are advised to try *"outlandish"* solutions).

"Prioritise.

"Select the most acceptable and workable solution.

"Practice the strategy.

"Evaluate the effective strategy and re-visit the problem cycle".

Page 66 provides quotations from the AfME 2003 Report: "*A number of quotes to assist with explanation of 'increasing as able' "*.

Page 67 is another blank record sheet entitled *"Energy Requirements"*.

Page 68 is a blank record *"(Baseline Sheet").* Participants are asked: "*What would be your own baseline at present?"* (the identical question was previously asked on page 15 of the Manual).

Page 69 is filled with a repeat of the incomprehensible diagram on page 9.

Page 70 is headed "*APT Review"*.

Page 71 is a section entitled *"Partners, Relatives and Friends Information"*.

Page 72 is entirely blank.

This Manual is woefully inadequate.

It is difficult to see how any of the participants would have found anything of real value in it to help them deal with a complex and life-wrecking disease.

The type of pacing universally reported by patients to be helpful is simple: listen to your body and do not push yourself.

It can be adequately explained to someone in five minutes and cannot be described as a "therapy".

Adaptive (or "*Adapted"*) Pacing Therapy appears to be an attempt to take this simple notion and stretch it sufficiently to fill a "Manual" for an MRC clinical trial.

The result is a deeply patronising and carelessly written document that is almost entirely devoid of meaningful content.

The authors have filled the pages with a repetitive collection of truisms, tautology, folk wisdom and cartoons.

The PACE Trial Protocol records that the patient charity Action for ME *"helped in the design of the APT Manual and have endorsed this version of pacing"*.

Members of AfME and the wider ME community may well question the value of AfME's contribution.

It is incomprehensible how such a document received approval from any Ethics Committees as a "therapy" in an MRC clinical trial.

Comments by participants in the PACE Trial

Message posted on 7th August 2008: *"I was randomly assigned to APT which I have been undertaking for about 8 weeks….I am interested in finding other people who have CFS/ME and been involved in this clinical trial. I have spoken to my local CFS/ME society but they just told me many have refused this trial".*

Message posted on 7th August 2008: *"…I have…worked with the physio at the ME clinic to do some sort of life timetabling, putting together a plan for the week where I can do one activity and have so much rest and do something else. All done by the clock and was about telling your body what to do rather than listening to it…I felt like an old woman who always had a cup of tea at 10am and always had dinner at 6pm and watched a certain programme on TV at a given time etc. I found I was just going through the motions…I was spending no energy doing anything that mattered…So I went back to sleeping when I feel like it and doing things when I feel good and not doing stuff when I don't…In 1997 when I was first ill I was really bad and stayed bad because people kept telling me I needed to exercise which made me worse…I am a little cynical about all ME treatment programme. There is NO cure for it so there is no point in expecting to magically get better. I feel I am the best person to sort out what I do and don't want to do…at the end of the day its down to you to sort it out".*

Message posted on 7th August 2008: *"PACE Trials is a clinical trial that has apparently been going for a number of years…APT which I was assigned to, involves finding your 'baseline'…that can be undertaken daily without you becoming exhausted. You are supposed to sustain this baseline at 70% of your usual capability….As I said in my earlier post my concern has been that my baseline is so way below what I was attempting to do previously…that I worry I may continue to decline rather than improve".*

Message posted on 7th August 2008: *"I didn't know it was called this but I have had a go at all the things you describe. My baseline was also very low and it cut out of my life all the things I enjoy".*

Message posted on 16th October 2008: *"I had the misfortune of seeing Dr X as well, the 'service' was utter rubbish. I was also part of their PACE trial, and it d----- near finished me off! The centre where it was held was only accessible from a very long corridor and several flights of stairs, the sessions were 5 hours long with a large part of that spent filling in forms…and ending with a very aggressive physio getting us all doing exercises which reduced a few people to tears. I was sent to an occupational therapist whose idea of pacing was to tell me I had to limit myself to standing for 5 minutes a day, as I was unable to walk every day…how am I meant to live like that? I found Dr X to be extremely unhelpful. Needless to say I removed myself from the programme".*

Another post said: *"I was pressurised by my family, GP and Dr X to go on it, and it seriously set me back. I only managed 3 sessions and was bedridden afterwards…most of the excessively long sessions was spent filling in questionnaires which were psychological assessments…I amused myself by giving fictitious answers…I felt the 'trial' was a joke…Needless to say, anyone who was bed/housebound were not included, so any 'results' were biased from the off…You have to wonder why one of the head honchos behind the trial is Professor X, an Honorary Consultant in Psychological Medicine…….I felt that very little was done to investigate what was actually wrong with me…I became very ill suddenly and pretty much couldn't walk overnight due to weakness and vertigo, my balance went and my hands were clawing"* (http://www.bbc.co.uk/ouch/messageboards/F3611783?thread=5747203).

Quotations from the doctors' SSMC Manual

This 48 page Manual consists of just 8 content pages, the remainder being nine appendices.

From the Minutes of the joint meeting of the Trial Steering Committee and the Data Monitoring and Ethics Committee held on 27th September 2004, it is a matter of record that Professor Peter White expressed concern that participants receiving only SSMC might interpret it as the 'go away' arm of the Trial.

The two "Contents" pages list the following:

"Background to the PACE trial"

"Patient Clinic Leaflet (PCL) – its use in SSMC"

"Timing of visits"

"SSMC – FAQ" (Frequently Asked Questions).

"Appendix 1……Appendix 9".

Standardised Specialist Medical Care (SSMC) is defined on page 4 of the Manual: *"SSMC is the standardised specialist medical care provided by the CFS/ME clinic doctor for patients who receive a diagnosis of CFS/ME".*

"SSMC includes:

- *A positive diagnosis of CFS/ME and an explanation of the condition that is consistent with the Patient Care Leaflet (see Appendix 2)* (emphasis added)
- *General advice on managing activity and stress and coping with the illness that is consistent with the Patient Clinic Leaflet (see Appendix 2)* (emphasis added)
- *The prescription of medication for specific symptoms (such as simple analgesia, hypnotics, antihistamines and antidepressants) if indicated and agreed with the patient*
- *Communication with…the participants* (sic) *General Practitioner*
- *Monitoring of the participants* (sic) *progress*
- *A copy of the assessment letter will usually be sent to the participant, so long as they wish to receive it".*

Thus the Fatigue Service clinic doctor is permitted to explain "CFS/ME" only according to the Wessely School beliefs set out in the Patient Clinic Leaflet and to give medical advice only according to the Wessely School beliefs.

Moreover, there is significant published evidence that antidepressants are ineffective in ME/CFS, for example, "Randomised, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome"; Jan HMM Vercoulen et al; Lancet 1996:347:858-861: *"Antidepressant therapy is commonly used (in CFS). However, there has been no randomised, placebo-controlled double-blind studies showing the effectiveness of antidepressant therapy in CFS. We have carried out such a study to assess the effect of fluoxetine (Prozac) in depressed and non-depressed CFS patients…There have been anecdotal reports that fluoxetine is poorly tolerated by patients with CFS. In our trial, 15% of fluoxetine-treated patients withdrew because of side effects, a higher withdrawal rate than in fluoxetine trials in depressed patients on the same regime"* and the authors concluded: "*Fluoxetine in a 20mg daily dose does not have a beneficial effect on any characteristic of CFS".*

There is also evidence that people suffer adverse reactions to such medication; indeed, intolerance to alcohol and medication (especially to drugs acting on the central nervous system) is a feature that the renowned neurologist Professor Charles Poser of Harvard described as pathognomonic of ME/CFS at the 1994 Dublin International Symposium held under the auspices of the World Federation of Neurology.

Page 5 of the SSMC Manual informs Fatigue Service clinic doctors that all participants will already have received the standardised patient clinic leaflet (which was to be handed out by the Fatigue Service clinics).

Fatigue Service doctors are told that: *"General advice on symptoms and activity management should be given. This advice should be compatible with that in the Patient Clinic Leaflet.*

"It is important that this advice:

- *Is as helpful as possible* (why does a doctor need to be reminded that medical advice should be helpful?)
- *Adequately reflects our uncertainty about aspects of management….for example, whether it is better to try and increase activity or to focus on pacing one self* (sic) *to manage available energy most effectively* (but participants in the CBT and GET arms of the trial – who will also be receiving "SSMC" – have been told that they can recover by increasing activity, so the doctor is told to give advice that directly contradicts the therapists' advice)
- *Does not contradict the principles of practice of any of the supplementary therapies, for example, does not argue against increasing activity or pacing* (so the SSMC doctor must explain any increase in symptoms after CBT/GET as a normal response to increased activity, but must explain the same symptoms after APT as pathological)
- *Is positive about the role of SSMC in advising and supporting the patient to create the best conditions for natural recovery* (the advice given to participants by the clinic doctor should not be "positive" – or negative – about the role of any of the interventions used in an on-going clinical trial).

Page 6 of the SSMC Manual states: "*The first SSMC appointment takes place within one month of randomisation. Participants will be seen by their SSMC doctor on a minimum of two further occasions in the 12 months after randomisation…Each session …would commonly last about half and hour"* (so participants -- including those receiving SSMC alone -- may see the Fatigue Service clinic doctor only three times for 30 minutes each time during their participation in the trial, a total of 90 minutes throughout the trial, which purports to constitute *"specialist medical care"*).

Page 7 states: "*SSMC sessions will be audiorecorded…The duration of each session can be taken from the audiorecording machine display and should be recorded in the medical notes, so that the total time spent in SSMC can be recorded… at the end of the participants* (sic) *SSMC".*

"Specific SSMC problems that might arise should be referred… to the centre leader, who can discuss the problem…with the SSMC lead who is Gabrielle Murphy or if necessary the relevant PI who is Michael Sharpe".

Page 8 gives instructions about "*Missed sessions…..If a participant drops out of SSMC it is essential that the Research Nurse is made aware of this immediately".*

"What SSMC is not:

"SSMC should be the usual medical care that one would reasonably expect clinic doctors experienced in the assessment and treatment of CFS/ME to provide (how can *"usual medical care"* be regarded as *"**specialist medical care**"?).*

- *…it is also essential that any advice given should not strongly favour any one particular illness management approach above another **and such advice must be compatible with any treatment that the participant is receiving** (APT, CBT, GET or SSMC alone)* (so the doctor is placed in the logically irreconcilable position of providing advice that must be consistent with two opposing models of the same disease, ie. a pathological model for APT participants *versus* a psycho-behavioural model for CBT/GET participants)
- *SSMC does not involve seeing the patient on a frequent basis to deliver a version of …APT, CBT and GET).*

Page 9 of the SSMC Manual lists some *"Frequently Asked Questions"*, included in which are:

"Q 1. The patient complains that SSMC alone is really no treatment – what do I say?

"A(nswer). Explain that 'more is not necessarily better'….People do recover naturally…(how does such advice qualify as *"specialist medical care"*?).

"Q 3. The patient has been randomised to a supplementary therapy (ie. to CBT, GET or APT) ***and tells me they would rather receive a different one – can I advise them?***

"A. Explain that we are running the trial because we do not know which therapy will be most helpful for which people and that is what the trial aims to find out…It may be helpful to point out that research shows that some treatments may take some time to have a positive effect, and can be helpful after the face-to-face therapy has finished" (is this subtle coercion for the participant to stay with an intervention that may be making them worse?).

"Other Questions:

"Q. What is my prognosis with SSMC alone?

"A. We do not know for certain, although specialist medical care provided by a fatigue clinic specialist has previously been found to be helpful in a scientific trial" (no further information or literature reference is provided, and the Trial Protocol states that only 10% of SSMC participants are expected to improve).

"Q. If SSMC alone can improve my symptoms how are you going to tell which therapy has helped those receiving SSMC and another therapy?

"A. ….We will look to see if more people get better with supplementary therapy combined with SSMC compared to SSMC alone".

"Q. If I am receiving no medication, what is it about SSMC that may help improve my symptoms?

"A. Advice and support of a doctor may be as good as any other treatment" (does such non-specific advice of a doctor constitute ***"specialist medical care"***?).

Appendix 1 starts on page 12 of the SSMC Manual and is entitled "*General Therapy Skills".*

"Knowledge and skills required: As well as a sound knowledge of the aetiology, epidemiology, consequences and available treatments of CFS/ME, a range of skills will also be necessary in order to help you engage and work collaboratively with these people (but on page 18 of this same Manual, it is stated: "*We don't know what causes CFS/ME"*, so how can the Fatigue Service doctor have *"a sound knowledge of the aetiology* -- ie. cause -- of "CFS/ME"?).

Essential skills are listed as: *"Engagement, Warmth and Empathy, Sensitivity, Collaboration, Positive reinforcement, Establishing confidence in you as a Specialist, Encouraging optimism, Engaging Participants in SSMC".*

"Engagement

"In order to engage the participant in treatment (exactly which component of SSMC constitutes "treatment" is not clarified) *it is important that the doctor conveys belief in the reality of their symptoms…People with CFS/ME are often sensitive to the over-emphasis of psychological factors. In order to maintain participant's* (sic) *engagement throughout treatment, it will be important that you continue to use a medical approach and do not imply that the*

illness is non-biological…" (this appears to be yet another reminder to the clinic doctor not to be fully open with the participant, despite the fact that the CBT and GET arms of the trial are predicated upon a psycho-behavioural model of "CFS/ME". It is also noteworthy that the authors have chosen the term *"non-biological"* as opposed to "psychological").

"Warmth and Empathy

"…

With this patient group (extending warmth and empathy) *is particularly important"* (why is it *"particularly important"* with this patient group more than any other?). *"It is therefore very important that you convey warmth and empathy at your first meeting"* (as noted in comments on other PACE Trial Manuals, this "*warmth and empathy"* are contrived and thus are insincere, which is misleading the participants). "*Acknowledging the difficulties they have encountered along the way in terms of their illness, whether related to its impact on their life or response from other health professionals, is important"* (the reason participants may have had difficulties with other healthcare professionals could be the consequence of the published views of the PIs about ME/CFS, illustrations of which can be accessed at http://www.meactionuk.org.uk/Quotable_Quotes_Updated.pdf).

"Sensitivity

"Although you cannot forever be thinking about whether or not you are going to offend them, it is worthwhile… trying to use language that is not going to be alienating…
For example, if a participant calls their illness ME don't attempt to challenge this, ME or CFS is an appropriate term to use" (but the Trial Protocol and Manuals state that the PIs are not sure if ME and CFS are the same illness).

"Positive reinforcement

"It is essential that you demonstrate positive reinforcement when you work with people with CFS/ME. Often, they will be very good at pointing out what they haven't achieved. It is therefore important that you empathise and are very positive about what they have achieved. Every session you should positively reinforce all of their achievements" (even if there have been no achievements?).

"Establishing confidence in you as a Specialist

"Establishing the participant's confidence in you as a therapist (so an SSMC "*Specialist"* becomes a *"therapist"*, further demonstrating editorial carelessness) *is important. This is likely to occur if you have knowledge of research into CFS/ME".* If the Fatigue Service doctors were aware of the research set out in Section 2 of this Report including immunological, neuroendocrine and cardiovascular research, as well as the acquired abnormalities in gene expression, they would surely be more circumspect about their involvement in the trial given that the biomedical research evidence invalidates the premise upon which it is based. Is it not misleading to describe the Fatigue Service doctors as "specialists" if they are not familiar with all the ME/CFS literature and if they do not inform participants of the existence of the biomedical evidence, or of the fact that many clinicians discourage ME/CFS patients from undertaking incremental graded aerobic exercise? Furthermore, as noted in Section 3 above, on 10th October 2003 it was confirmed by Dr Gabrielle Murphy that the "CFS" Clinic at St Bartholomew's Hospital was no longer an immunology clinic but a psychiatric unit – see http://health.groups.yahoo.com/group/MEActionUK / message 15999. Of the original twelve Fatigue Service Centres, seven were under the auspices of mental health professionals.

"Encouraging optimism

"…

it is important that you encourage optimism about the progress they have made (how is this materially different from *"positive reinforcement"*?). *There is in fact some evidence that patients with symptomatic complaints* (*"symptomatic complaints"* is medical shorthand within liaison psychiatry for "all in the mind") *are more likely to improve if you encourage a positive expectation"* (invoking a "*positive expectation"* is called the placebo response, which would normally be controlled for -- not actively sought -- in a clinical trial).

"Engaging Participants in SSMC

"Do's (sic)*:*

- *Ask the participant what they would like to be called when you first meet*
- *Discuss the agenda for the appointment*
- *Show empathy, warmth, sensitivity and understanding* (it is reasonable to question how such "manualised" and programmatic qualities can be genuine)
- *Give a clear explanation of the diagnosis using the participants own words where possible*
- *Be very positive about participants* (sic) *attempts to help themselves to overcome their CFS/ME*
- *Give participants the opportunity to discuss any fears or worries in relation to treatment* (does this include their fears or worries about CBT or GET?)
- *Tell the participant that you will look forward to seeing them over the coming year* (again, these are "manualised" and programmatic instructions: if the doctor does <u>not</u> look forward to seeing a participant in the Fatigue Service clinic, is the doctor being encouraged to be untruthful?)
- *Use language that participants will understand.*

"Don'ts

- *Get into an argument with the patient about their beliefs about the illness* (this seems to indicate that the PIs are anticipating patients who believe they are physically ill but have a concern that clinic doctors view "CFS/ME" as a psychiatric disorder)
- *Minimise symptoms by saying something like 'we all get tired'*
- *Imply that the symptoms are imaginary* (if "specialists" have to be given such a written injunction, then once again this seems to be evidence that the PIs anticipate that the Fatigue Service doctors may inadvertently reveal that they do not believe "CFS/ME" is a physical disease).

<u>Appendix 2: (the Patient Clinic Leaflet)</u>: this starts on page 16 of the SSMC Manual.

Those charged with distributing this leaflet via the Fatigue Service clinics are reminded in their instructions that ***"WHEN PRINTING*** *print on HEADED PAPER from your CLINIC….please do not use UNHEADED PAPER. DO NOT GIVE THIS COVER SHEET TO PATIENTS".*

This leaflet has been referred in Section 3 of this Report; it can be accessed at http://pacetrial.org/trialinfo.html

Some illustrative statements in the leaflet include the following:

"Symptoms often get worse if you exert yourself" (post-exertional relapse is <u>the</u> cardinal feature of ME; if a person does not experience post-exertional relapse, ME cannot be diagnosed).

"*People with CFS/ME are sometimes afraid that people will not believe that their symptoms are real. In this clinic we believe CFS/ME is a real illness"* (this is misleading because participants are likely to understand *"real"* to mean "physical" disease, but the CBT/GET arms of the trial are predicated on the assumption that there is <u>no</u> physical disease and that "CFS/ME" symptoms are the consequence of aberrant beliefs and behaviour).

"How is CFS/ME diagnosed?

"There are several descriptions of the typical symptoms and all these definitions agree that people with CFS/ME:

- *have the main symptom of fatigue that is often made worse by exertion*
- *often have other symptoms – including headaches, sleep disturbance, sore throat, muscle or joint aches and pain, and tender lymph glands* (this is wrong and misleading: apart from the Wessely School's Oxford criteria that were used in the PACE Trial, all the other case definitions require the presence of other symptoms; they are not optional).

"What causes CFS/ME

"We don't know what causes CFS/ME (but on page 12 of the SSMC Manual – to which the Patient Clinic Leaflet is attached as Appendix 2 -- doctors are required to have *"a sound knowledge of the aetiology"* of "CFS/ME"), *although there are various theories – well-informed scientific ideas that have yet to proved or disproved"* (what scientific theories does the PACE Trial attempt to prove or disprove? None. Vincent Deary -- described in the PACE Trial literature as a "*First wave therapist (CBT)"* and as a contributor to the treatment design -- describes the "CBT Model" as a useful trial-and-error way of approaching a problem, but this is not a scientific theory. The Wessely School ignore the scientific evidence that does not support their own model, which is the antithesis of science).

"There is evidence that CFS/ME can be triggered by certain infections, most of them viral. There is no strong evidence that these infections are maintaining factors in CFS/ME" (in the light of the biomedical research evidence, many clinicians and medical researchers accept that ongoing infection causes and maintains ME/CFS and participants should be told this).

"Minor abnormalities of the immune system are commonly found in people with CFS/ME" (this point has been addressed in Section 3 above at point 13 under "Apparent misrepresentation in the PACE Trial?".

Other alleged causes of "CFS/ME" listed include *"Sleep disturbance"*; *"Doing too much and doing too little"*; *"Loss of physical fitness and strength"*, for none of which is any proof provided.

"Food intolerance

"Some people with CFS/ME say certain foods make them worse. But there is no good evidence that food intolerance triggers or maintains CFS/ME" (it is notable that anything "physical" such as infection or food intolerance is dismissed due to an alleged lack of good evidence, but behavioural aspects, for example, "boom and bust" behaviour, which also lack good evidence, are stated as though they were proven fact. This is a very biased assumption).

"Other possible factors

"Many other things are said to be linked to CFS/ME, and some get a lot of publicity – even though nobody has proved they are factors in CFS/ME. These include magnesium deficiency, overgrowth of the yeast Candida in the bowel, and low blood sugar" (these have all been empirically shown to occur in ME/CFS; again, the dismissal of these physical factors by the implicit slur that they "*get a lot of publicity"* is notable).

"How soon will I get better?

"Most people with CFS/ME improve over time with treatment" (there is no evidence to support such an assertion: the Chief Medical Officer's Working Group Report on "CFS/ME" states that there is no cure (CMO's Working Group Report: January 2002: 4.4.2.2:48) and the Department for Work and Pensions' own Disability Handbook, May 2007, Chapter 16, entitled "The Chronic Fatigue Syndrome" states: "***There is no cure***" (16: Management: 16).

"Specialist Medical Care

"Specialist medical care is the most usual treatment for CFS/ME, and it helps many people improve" (first, SSMC is far from being "specialist" medical care; secondly, the Trial Protocol states that only 10% of participants are expected to make any improvement after one year of SSMC, so it is misleading to inform participants that *"it helps many people improve"). You get a confirmed diagnosis, an explanation of why you are ill and general advice about managing your illness"* (how can the SSMC doctor provide an explanation of why the participant is ill, given that earlier in the same leaflet it is acknowledged that: *"We don't know what causes CFS/ME"*?).

"Complementary and alternative therapies

"Some people…say they benefit from them …we cannot recommend them". As noted in Section 1 above, this concurs with the known views of the Wessely School: section 9.20 of the 1996 Joint Royal Colleges' Report (CR54) states: "*We have concerns about the use of complementary therapy and dietary interventions"*, a statement that is in accordance with the published views of HealthWatch, of which Wessely is a*"leading member of the campaign"* (see Section 3 above).

"Which treatments are available in this clinic?

"We offer specialist medical care, as described above. We may also offer you these therapies as well as specialised medical care: adaptive pacing therapy; cognitive behaviour therapy; graded exercise therapy…You may also have the option in this clinic of putting yourself forward for the PACE Study, which is described below. This may increase your treatment options" (there were only four options available in the PACE Trial – SSMC, APT, CBT and GET, so quite how volunteering for the trial increased treatment options is not known; furthermore, it is understood that the West Midlands Multi-centre Research Ethics Committee required the sentence "*This may increase your treatment options*" to be removed from later versions of the Patient Clinic Leaflet -- there were at least nine versions -- because they deemed it coercive).

Appendix 3: Participant information sheet for PACE trial (page 23 of the SSMC Manual)

"Invitation to join the PACE trial

"We are inviting you to help us with our research. But before you decide whether or not you want to join our study, you will want to know what we are doing, why we are doing it – and what we would be asking you to do. This leaflet will answer most of your questions….Take as much time as you need to decide whether or not you want to help us. If you don't want to join our study, this will not affect your NHS care" (this promise has been disputed by patients; importantly, the leaflet does not explain that two of the therapies are based on the assumption that people with "CFS/ME" suffer from a psychiatric disorder).

"***What is your study for?***

"…We also hope to learn why successful treatments work" (this states that it is already known that certain treatments used in the trial are successful and it is only the mechanism of how they work that needs to be determined by the trial, and therefore could be viewed as an inducement to participate because patients are understandably desperate to get better) *and whether different people need different treatment. Finally, the study will compare how much these treatments cost, to see if they are a good way of spending NHS money"* (it could be argued that participants should have been explicitly told that the trial is collecting data about State and insurance benefits, given (i) the highly unusual involvement of the Department for Work and Pension, this being the only clinical trial the DWP has ever funded; (ii) that it provides detailed back-to-work information for participants on two arms of the trial; (iii) that it aims to test the Wessely School hypothesis that *"being in*

dispute/negotiation of benefits or pension" is a predictor of a negative response to therapy. Later in the leaflet, under "***Will you keep my details confidential?",*** participants are told *"Occasionally, other researchers will need to see your notes…an audit might be run by …one of the organisations funding our study"* (so the DWP can have access to participants' confidential medical notes as well as to the psychological questionnaires and personal financial data obtained by the PIs. The majority of people with ME/CFS experience considerable difficulty when claiming benefits, which is understood to be linked to the fact that the DWP is known to be targeting people with ME/CFS to remove them from benefits).

"Whichever treatments are shown to be best, we expect they will become more widely available across the country" (many people believe it to be a foregone conclusion that CBT and GET will be "shown" to be effective and that even more Fatigue Service psychiatric clinics will be opened. As noted above in the comments on the GET Therapists' Manual, Professor Peter White is on record as asserting that GET should apply even more to those who are severely disabled: on page 24 of that Manual, they assert: "*Due to greater levels of inactivity in the more severely affected group, the deconditioning model should apply equally if not more to these patients"*). How anyone could think this would be an appropriate intervention for people like the late Lynn Gilderdale defies reason (http://www.timesonline.co.uk/tol/life_and_style/health/features/article6998742.ece) but, impervious, one psychiatrist who views ME as a psychiatric disorder declined to contribute to the article: "***My views are too controversial to publish"***.

Next come brief descriptions of the four interventions: SSMC; APT; CBT and GET, none of which even mentions any of the extensive pathology that is known to exist in ME/CFS.

"Do I have to join your study?

"No. You decide whether or not you want to help us" (this is expressed in emotive and coercive language and may make the person feel guilty if they decide they do not *"want to help"* other people with ME/CFS, especially as they have been told that certain PCE Trial therapies are already known to be successful). *Even if you sign the forms, you can still leave the trial at any time – and you won't even have to give us a reason"* (this cannot be true, because anyone who wants to drop out will receive an immediate telephone call from the Centre leader; certainly it is known from participants who have withdrawn just how much pressure was put on them to remain in the trial, which can only be described as coercion).

"***What will happen if I join your study?"*** Illustrations include the following:

"1. We ask you questions and measure your fitness

"A six minute walking test will tell us how physically fit you are" (this is not the case; only sequential testing will accurately measure the physical ability of people with ME/CFS). *Your nurse will give you a movement monitor…and ask you to wear it on your ankle for one week".*

"2. You find out whether you are suited to our study

"…A week later, you will bring back the movement monitor and the questionnaires. Your nurse will ask you more questions, including how CFS/ME has affected you financially (would a research nurse in any other MRC clinical trial ask participants with a classified neurological disease how it had affected them financially?) *and ask you to do a two-minute step test to tell us more about how fit you are* (a two-minute step test cannot provide clinically useful information for people with ME/CFS). *If we decide you should not be in our study, your nurse will refer you back to your clinic doctor".*

"3. A computer randomly allocates a treatment for you"

"4. Everyone sees their research nurse three more times

"We will post you our questionnaires, so you can fill them in at home…Filling them in will take about an hour…You won't need to wear the movement monitor again" (lack of post-intervention objective monitoring would seem to be inexcusable in an MRC clinical trial that purportedly aims to determine how effective are the interventions being studied: compared with the heavy commitment of 14 sessions of CBT/GET plus a follow-up session over a full year and the incessant keeping of diaries and record sheets, the wearing of an actigraphy monitor for one week involves no work, and without this data, no meaningful conclusions can be drawn from the trial).

"Could joining your study make my condition worse?

"…Some patient surveys suggest CBT and GET can make symptoms worse – but experts (the Wessely School refer to themselves as experts in "CFS") *believe this happens when the therapy is not used properly or when there isn't good professional supervision"* (this is misleading: in the light of the biomedical research evidence, many doctors consider that CBT and especially GET are contra-indicated in ME regardless of how well they are delivered; moreover, as addressed in Section 1 above, the large AfME 2008 survey found that there was no significant difference between the number of adverse reactions suffered by those who undertook a programme of GET under an NHS specialist (31.1%) compared with those who undertook such a programme elsewhere (33.0%), which undermines the validity of the reassurances in the leaflet).

"This is a national study. Here is a full list of the participating NHS centres" (it is notable how many of the Centres are Mental Health Trusts).

Appendix 4: Managing Potential Difficulties (page 33 of the SSMC Manual)

These are essentially the same points that have been addressed above, ie. "*The participant has a fixed physical attribution of illness"; "The patient feels that a cause has been missed and wants further investigations"; "Patient requests to withdraw from the trial"; "Cancellations, DNAs* (did not attend) *and missed appointments"; "Telephone calls from patients".*

In relation to *"The patient has a fixed physical attribution of illness"*, the Appendix to the SSMC Manual states: "*If participants are insistent that there is an ongoing 'physical' problem…it is important that you acknowledge that their illness is real* ***but its effects can be reduced by the way they manage it****"* (emphasis added).

There is no evidence to support such as assertion; moreover, how does this accord with page 9 of the CBT Therapists' Manual, which states: "*The assumption of SSMC is agnostic to the nature of the cause and best treatment of CFS/ME"*, so why would it be a potential difficulty if the patient has a "*fixed physical attribution"* when the SSMC doctor is supposed to be neutral?

What this demonstrates is that the PIs do not believe that "CFS/ME" is a physical disease and the clinic doctors probably hold the same beliefs, otherwise this reminder would not be necessary.

Appendix 5: information for participants about benefits (page 35 of the SSMC Manual)

This appendix includes information on *"Work, Courses and Resources"; Information for people who are in receipt of benefits"; "New Work rules for people in Incapacity Benefit"; "Income Protection"; "Disability employment advisors"; "Work Care"; "Jobcentre Plus"; "New deal for disabled people"; "New Deal 50 plus"; "Linkline"; "Learndirect courses and centres"; "Voluntary work"; "Citizens' Advice Bureau"* (sic).

Appendix 6: Summary of Therapies (page 42 of the SSMC Manual)

This is similar to but slightly different from the summary contained in the Therapists' Manuals.

Appendix 7: CGI for SSMC Doctors (page 43 of the SSMC Manual)

This Clinical Global Impression (CGI) purports to record the *"global impression of change scale"* achieved by the participant during the PACE Trial.

It asks questions such as "*Overall, how much has the participant changed since the start of the study?"; "How well has the participant adhered to both medical management and advice – did the participant actually implement what had been negotiated in the sessions?"; "To what extent did the participant accept the principles underlying the management advice they were given?"; "How many treatment sessions with you* ***in total*** *has the participant received?"; "How many planned sessions did NOT occur?"; "How many unplanned phone calls took place?"; "How many sessions were attended by a relative (not partner) of the participant?"; "How many sessions were attended by a friend of the participant?"; "How many sessions were attended by the participant's partner?"* (the CGI rating scales are commonly used measures of symptom severity, treatment response and the efficacy of the treatment **for patients with mental disorders** [W.Guy, editor, ECDEU Assessment, 1976; US Department of Health, Education and Welfare]. Many researchers regard it as too user-subjective. Why are the PIs using a rating scale commonly used in mental disorders?).

Appendix 8: Medical screening SOP -- Standard Operating Procedure (page 45 of the SSMC Manual).

This covers *"Assessment; History; Examination; Investigations; Common medical exclusions; Temporary medical exclusions; Psychiatric exclusions".*

Appendix 9: Contra-indications and Cautions for Trial Treatments (page 47 of the SSMC Manual)

This lists *"Absolute Contraindications to the PACE Trial"* and *"Potentially allowable conditions (To be discussed with Centre Leader and Physiotherapist)".*

This SSMC Manual appears to be entirely based on the Wessely School belief that "CFS/ME" is a psychiatric disorder.

Any participant entering the PACE Trial in the expectation of receiving "specialist" medical care may well find themselves questioning if care from a consultant who ignores the significant biomedical evidence about the disease and who is able to provide only "general advice" is deserving of the appellation "specialist."

As stated above, the Principal Investigators expect SSMC to help only 10% of participants; in any other medical discipline this would be considered unacceptable.

Right at the start of the PACE Trial selection process, Fatigue Service doctors failed to inform potential participants of the extensive biomedical research evidence that invalidates the Wessely School's behavioural model of ME/CFS, or of the potential risks of GET.

This is deemed by many people to have lured unwitting patients into entering an MRC clinical trial under false pretences and some consider that it amounts to professional misconduct that is pivotal to the whole trial.

CONCLUSION

To quote from a recent article in The Times: *" 'It's like a battlefield,' says Dr Neil Abbot, operations director of ME Research UK. He describes the lot of the ME patient as a 'Kafkaesque nightmare'… Stephen Holgate, professor of immunopharmacology at the University of Southampton, chairs the Medical Research Council's expert group on CFS/ME. 'As a clinician who sees patients with this group of diseases I recognise there's a real thing here, it's not all psychiatric or psychological', he says. 'Unquestionably in some of these patients there are abnormalities and biochemical changes in the brain, the central nervous system, the spinal cord or the muscles'. Such is the hostility engendered by the debate that medical professionals who view ME as a psychiatric disorder declined to contribute to the article. In 2008-09 the MRC spent £728,000 on ME/CFS out of a total research budget of £704.2 million. The MRC is ready to commission more research on ME, he says, but the stigma and scepticism associated with the condition do not make it an attractive option for top quality scientists. 'The debate is so polarised that scientists are frightened to get involved', says Holgate. 'My aim is to get everyone round the table, so that instead of people throwing bricks at each other we can agree on the priorities, get some quality proposals written up and build confidence in the research community. The need for more research is urgent because what's happening now is unacceptable for patients and it's costing the Government a lot of money' "* (http://tinyurl.com/yeha84b).

Notwithstanding, the Wessely School remain certain that "CFS/ME" is a primary psychiatric disorder and the PACE Trial is predicated on this belief, despite international concern that broadening the case definition to include psychiatric "fatigue" (as the Oxford criteria do) can only obfuscate matters: *"During the last 15 years, estimated rates of CFS have dramatically increased in both Great Britain and the United States.* ***We suggest that the increases in both the United States and Great Britain are due to a broadening of the case definition to additionally include cases with primary psychiatric conditions. Using a broad or narrow definition of CFS will have crucial influences on CFS epidemiological findings, on rates of psychiatric co-morbidity, and ultimately on the likelihood of finding a biological marker****"* (LA Jason et al; How Science Can Stigmatise: the Case of Chronic Fatigue Syndrome. JCFS 2008:14:4:85-103).

The need for more exact selection of participants has been highlighted by ME/CFS international expert Professor Nancy Klimas from Miami, most recently on 21st January 2010: *"…when scientists define an illness, they do so to go after the group that has the illness,* ***trying to exclude as many similar illnesses as possible****"*(http://tinyurl.com/yex98m8**)**.

This is the exact opposite of what has occurred in the PACE Trial, which intentionally amalgamated many different states of what the PIs continue to regard as "*medically unexplained fatigue"*; as noted in Section 1 above, Professor Sharpe is on record as affirming: ""*We* ***want*** *broadness and heterogeneity in the trial"* ("Science and ME", International Science Festival, 9th April 2004, Edinburgh).

This was further confirmed by Professor Peter White: "*…we need to widen the net to capture all those people who become so chronically tired…that they can't live their lives to their full potential"* (Population Health Metrics 2007:5: 6 doi:10.1186/1478-7954-5-6). By combining all those who become "*chronically tired"* specifically in order to increase "*generalisability"* of their own anticipated findings, the Wessely School render the results of the PACE Trial inapplicable to those with true ME.

At the Institute of Clinical Research & European Medical Writers' Association Joint Symposium held on 24th February 2009, Abhijit Chaudhuri, Consultant Neurologist and ME/CFS specialist, spoke on "Recruiting Patients: Trials and Tribulations" and said that the most important issues for investigators and trial participants are whether the trial is asking a relevant and scientifically sound question, and the risk to benefit ratio of taking part. He also said that for a successful trial, it was essential that the protocol had ***"well-designed inclusion and exclusion criteria"***, which appears not to be the case with the MRC PACE Trial, given the intention to use such a broad definition of unspecified "chronic fatigue".

There can be no doubt that, for patients with ME/CFS as distinct from those suffering from chronic "fatigue", neither CBT nor GET is effective, otherwise -- after 20 years of the implementation of the Wessely School's interventions -- everyone would by now be cured.

Given the substantial and significant evidence that ME/CFS is not a psychiatirc disorder, it is disturbing that the Wessely School continue to place so much emphasis on trying to change patients' (correct) cognitions.

In this respect it is notable that Professor Sir Mansel Aylward (he was knighted in the Queen's 2010 New Year Honours List; in 2005 he was elected to the Queen's Birthday Honours Committee and in September 2008 he was formally re-appointed for a further three years) is to give a lecture on 17th May 2010 entitled "The Power of Belief: Harnessing its Potential to Bring about Behavioural and Cultural Change around Health, Illness and Work".

The pre-conference workshop is to be given by Anthony McLean on 16th May 2010 and is entitled ***"How to Ethically Influence Others"***. McLean was trained by Dr Robert Cialdini, a social psychologist and author of "Influence: Science and Practice" (a book that considers why people comply with requests) and "Yes! 50 Scientifically Proven Ways to be Persuasive". McLean will identify and explain the six universal principles of persuasion that allegedly produce *"lasting…and strong, long-term change"*.

According to the pre-conference publicity, the dominant theme of Aylward's presentation is to be: *"**how belief and belief networks and ways of modifying them play a cardinal role in securing attitudinal, behavioural and cultural change in both the individual and society**. Prof Aylward will illustrate this by describing the outcomes of his research and how belief networks operate in the spheres of health, illness and disability and impact on return to optimal functioning and (re-)entering engagement in work.*

"*Over the past decade evidence has emerged that biopsychosocial factors, such as beliefs, have a fundamental role in the presentation of illness, recovery, and the probability of return to as well as retention in work. Ill-health and disability…may be meaningfully explained in terms of psychological and socio-cultural factors…**Professor Aylward's keynote address will also provide an understanding of public policy initiatives for large scale modifying of belief networks in society"*** (http://www.arpa.org.au/Conference/PreConferenceWS.aspx), a sinister-sounding policy that if applied in the UK may – indeed perhaps ought – to strike fear in the heart of every person with ME/CFS, given the knowledge that they have been specifically targeted by the DWP for the removal of state benefits that are essential for basic survival.

In contrast, reviewing Barbara Ehrenreich's recent book "Smile or Die: How Positive Thinking Fooled America and the World", the respected Woman's Hour host Jenni Murray is emphatic: ***"To actually follow a philosophy that says that the way you think, the way that you operate, is what can make you better, is just such a cheat and a lie"*** (http://www.guardian.co.uk/theguardian/2010/jan/16/womens-hour-jenni-murray).

As American researcher Dr Jacob Teitelbaum points out on his website:

"Is Cognitive Behavioural Therapy harmful in (ME)CFS? Unfortunately, some of those using it for (ME)CFS believe that they have to convince the patients that their disease is not real. Besides being abusive, this approach is insane and often makes the patients worse. Nonetheless, it can save the insurance companies tons of money"
(http://www.endfatigue.com/health_articles_c/Cfs_fm-is_cognitive_behavioral_therapy_harmful_cfs.html).

Commenting on the UK study that failed to find any evidence of XMRV in almost 200 patients with "CFS" from Professor Wessely's Fatigue Service Unit in London, Dr Judy Mikovits noted: "*They paid to have their study published in the Public Library of Science*", adding that she suspects insurance companies in the United Kingdom are behind attempts to sully the findings of her Reno study (Co-Cure RES, NOT: 23rd January 2010).

Commenting on an article in The Economist, on 10th January 2010, physician Dr M White wrote:

"I have spent more than 20 years treating these sick people and I can tell you that they are indeed terribly sick. My sickest people are the ones with CFIDS/ME, not the ones with HIV or even cancer. I have treated everyone from young children to other doctors, lawyers, and even psychiatrists - and all make the same statements, all have tests and even brain SPECTS that come back so similar that I am astounded. ***So, as a doctor treating these terribly ill people I have not given Simon Wessely and his followers any attention. IF any of these people were to actually see and treat the sick, they too would know that this is physical and not an emotional disease where one cannot cope.*** *My patients are a hardy bunch and I am rather impressed with their abilities to withstand the punches that life, society and the medical community lobs at them time and again. I must say that I don't believe I could withstand all that my sick people put up with. Do continue to cover this terrible disease but do so in a manner of respect….You might also use solid data to make your case - God knows that there are reams of data out there and easily obtainable (and validated by numerous researchers and labs")*
(http://www.economist.com/node/15211401/comments?page=1&sort=asc).

Over 80 people took part in the 3-year Chief Medical Officer's Working Group on CFS/ME (1998-2001); details were available on 3,074 patients and the summarised results showed very clearly that the most helpful strategies were pacing activity with rest (90%); the least effective strategy was CBT, which made no difference for 55% and made things worse for 22%, and the most harmful strategy was GET, which made things worse for 48%.

It was the Wessely School psychiatrists who, led by Professor Peter White, would not accept the organic evidence and as a group walked out, refusing to sign or endorse the final report because they vehemently disagreed with its conclusion -- they wanted the report to conclude that "CFS/ME" is a psychiatric disorder and they objected to the report's recommendation of pacing. Despite this, it is now the very same psychiatrists who have been awarded unprecedented public funding to pursue their psychologically-focused research and who are calling the shots in the new Government-funded Fatigue Service Centres.

It is time that these psychiatrists took notice and listened to what patients and medical scientists keep telling them.

How can symptoms that clearly indicate significant pathology be so persistently dismissed and sufferers be so denigrated, given the nature and severity of the problems presented? These include not only the watered-down subjective description of "fatigue", but symptoms of organic pathology that ought to be unmissable by any doctor.

It is, of course, the Wessely School's view that the multiplicity of symptoms in ME/CFS confirms their belief that it is a somatoform disorder, but if these psychiatrists do not acknowledge and identify such serious symptoms as organic, they are not seeing patients with ME (so therefore should not describe their studies and results as pertaining to those with ME).

It seems beyond dispute that it is psychiatric bias and vested commercial interests that drive current policies about ME/CFS: as Hyde noted in 1992: ***"This failure to return to the literature haunts the very basis of their definition***" (The Clinical and Scientific Basis of Myalgic Encephalomyelitis Chronic Fatigue Syndrome; The Nightingale Research Foundation, 1992), a statement that is equally valid 18 years later, because it is the continued failure to heed the literature that underpins the current unacceptable situation.

As there is an ever-increasing body of evidence of an organic pathoaetiology, on what logical grounds do these psychiatrists remain unconvinced that ME/CFS is an organic disease and insist that it is merely a "mistaken illness belief"?

As Dr Jonathan Kerr from the UK noted: ***"One valuable approach that has not been widely adopted in the management of (ME)CFS patients is to exhaustively investigate such patients in the hope of identifying***

evidence for a specific persistent infection" (LD Devanur, JR Kerr. Journal of Clinical Virology 2006: 37(3):139-150), but the Wessely School have consistently argued that no investigations should be performed to confirm the diagnosis (for example, in the Joint Royal Colleges' Report on CFS, CR54, 1996). Following publication of that report (which was internationally condemned for its extreme psychiatric bias and of which Professor Simon Wessely was understood to be the prime mover), the Editor of the Lancet, Richard Horton, courageously spoke out against it: "***The college representatives interpreted every piece of evidence pointing to a biological cause in a negative light. Medical paternalism seems alive and well in Britain today***" ("Why doctors are failing ME sufferers". Dr Richard Horton. Observer Life, 23 March 1997).

There *is* now laboratory evidence of organic disease in ME/CFS, yet these psychiatrists continue to dismiss or ignore it and, at a cost to UK taxpayers of over £11.1 million, pursue their own belief that "CFS/ME" is a functional somatic syndrome that is amenable to, and even curable by, behavioural modification techniques.

That the Wessely School remain intransigent in their beliefs about ME/CFS can be seen, for example, in the American Family Physician, a peer-reviewed journal of the American Academy of Family Physicians (which is one of the largest groups of physicians in the US). The issue of 1st November 2005 (volume 72, no. 9) featured CFS in the section "Clinical Evidence Concise", this being a section that purports to provide evidence-based continuing medical education (CME) for the credits that are required to be obtained by all physicians to demonstrate their up-to-date medical knowledge.

Articles in "Clinical Evidence Concise" purport to summarise current knowledge about a disorder and are used in "best practice" guidelines.

In that particular issue, the authors of the CFS article were Steven Reid, Trudie Chalder, Anthony Cleare, Matthew Hotopf and Simon Wessely. What was so disturbing was that the article was a re-run of the same authors' paper in the BMJ of January 2000, which itself was a shortened version of their article in the second issue (December 1999) of "Clinical Evidence", a BMJ Publishing Group Review. For these authors to have published it again six years later demonstrates their refusal to pay any heed to the wealth of biomedical evidence about ME/CFS that had been published in the intervening years.

As Jill McLaughlin noted on http://health.groups.yahoo.com/group/MEActionUK/ : "*This is what is being distributed to physicians all over the country who legitimately use evidence-based medicine to treat (or in this case, shall we say, mistreat) patients. We cannot always rail at doctors when this is the information that they are receiving in mainstream, peer-reviewed medical journals".*

It is known that, although not yet published, the results of the FINE Trial (the sister trial to the PACE Trial that was funded entirely by the MRC) have shown that "pragmatic rehabilitation" (PR, based on CBT/GET) was minimally effective in reducing fatigue and improving sleep only whilst participants were engaged in the programme and that there was no statistically significant effect at follow-up. Furthermore, pragmatic rehabilitation had no statistically significant effect on physical functioning; equally, its effect on depression had diminished at follow-up. Moreover the other intervention being tested ("supportive listening" or SL) had no effect in reducing fatigue, improving physical functioning, sleep or depression.

Notwithstanding, the investigators are already seeking further funding to test their hypothesis that providing more sessions might improve the effectiveness of pragmatic rehabilitation which they state "*will inform the next phase of our work….The first phase of this work will be in conjunction with the Greater Manchester CFS Service"* (two FINE Trial case histories can be found in Appendix VIII).

Is this another illustration of the Wessely School's determination not be deterred by evidence that does not suit their own "evidence-based" agenda? To the on-going detriment of people with ME/CFS, it appears to remain the case that, supported by the MRC, the Wessely School continue even now to disregard the empirical evidence and to pursue their own behavioural model of "CFS/ME".

In "Letter from America" on 31st December 2001 on the BBC's World Service, Alistair Cooke -- whilst not referring to ME/CFS -- encapsulated the problems that have for so long beset the ME community:

*"By shouting the word often enough they hope to turn it into a reality. It's a case of what the poet William Empson called **'incessant belief labouring to create its object'**. How true. And how spectacularly unscientific".*

Central issues of concern about the MRC PACE Trial

The central issues of concern about the PACE Trial are issues of flawed methodology including (i) misleading participants about the nature of the disorder being studied and (ii) misinforming them about the efficacy of the interventions.

Illustrations of flawed methodology include the following:

(1) The prime methodological flaw is the use of the all-embracing Oxford entry criteria, which has been addressed above; **essentially, the Principal Investigators have used entry criteria that do not define the population they purport to be studying.**

The entry criteria for the PACE Trial expressly exclude those with neurological disturbance but specifically include those with psychiatric disorders and the suggested comparison groups include those with neuromuscular disorder. If the entry criteria were correctly applied, patients with true ME should have been screened out of the PACE Trial. This did not happen, because the Wessely School do not accept the WHO classification of ME as a neurological disorder. However, the mere fact that a group of psychiatrists does not accept that ME is a neurological disorder is insufficient reason for them to misapply their chosen entry criteria.

(2) It is a basic rule of any clinical trial that participants are not told during the trial how effective is the intervention that they are receiving.

It should never be suggested to trial participants that the intervention they are undertaking is a cure unless it is certain that it is indeed curative, in which case there would be no need for a clinical trial to prove the efficacy of the intervention.

The Principal Investigators are on record as stating that full recovery is possible with CBT/GET: Professor Michael Sharpe asserted *"There is evidence that psychiatric treatment can be curative"* (BMB 1991:47:4:989-1005) and Peter White – using *"the General Practice Research Database to show that social factors affect prognosis in CFS"* has unambiguously asserted *"recovery from CFS is possible following CBT….Significant improvement following CBT is probable **and a full recovery is possible**"* (Psychother Psychosom 2007:76(3):171-176).

To mislead patients by suggesting that a cure can be expected when there is no such certainty is in breach of the General Medical Council Regulations as set out in "Good Medical Practice" (2006):

"Providing and publishing information about your services – paragraphs 60-62

62. *If you publish information about your medical services, you must make sure the information is factual and verifiable.*

63. *You must not make unjustifiable claims about the quality or outcomes of your services in any information you provide to patients. It must not offer guarantees of cures, nor exploit patients' vulnerability or lack of medical knowledge".*

To imply that patients can recover from ME/CFS if they would only follow the psychiatrists' recommended regime of CBT/GET offers false hope: the recovery statistics simply do not support such a belief.

The promise of a likely cure through CBT and GET is a cause for concern and Professor Peter White has been warned on numerous occasions about making such a promise.

For example, in his submission about the NICE draft Guideline (24th November 2006, comments on chapter 6, page 308), Peter White objected to NICE's position concerning recovery from "CFS/ME"; referring to the draft Full Guideline 188 6.3.6.16, he was unambiguous: ***"These goals should include recovery, not just exercise and activity goals"***, to which the NICE Guideline Development Group's response was equally unambiguous: "*The statistics indicate that total recovery is relatively rare and the GDG felt that to include recovery as a goal may lead to disappointment"* and, as noted above, the Final Guideline was clear: "***The GDG did not regard CBT or other behavioural therapies as curative*** *or directed at the underlying disease process"* (Full Guideline, page 252).

Not only did the Chief Medical Officer's Working Group Report of 2002 state that there is no recovery from "CFS/ME" (4.4.2.2.48), from which Peter White and Trudie Chalder resigned because "*….some clinicians believed that the report over-emphasised the severity and chronicity of CFS to the extent of* ***suggesting that recovery was unlikely, when the evidence shows that not to be true****",* nor did NICE accept Peter White's belief that he can cure people and – perhaps surprisingly, given that he is lead advisor on "CFS/ME" -- neither does the Department for Work and Pensions. The Disability Handbook (2nd edition, 1998) is being revised chapter by chapter, and Chapter 16 ("The Chronic Fatigue Syndrome") of May 2007 states: "***There is no cure***" (16: Management: 16).

As the issue is so important, it is worth reiterating that:

- according to US statistics provided in August 2001 by the Centres for Disease Control CFS Programme Update, only 4% of patients had full remission (not recovery) at 24 months

- in 2005, the message was: ***"The bitter, unpalatable reality is that ME/CFS patients can be pro-active, they can have a good attitude, they can try various drugs and non-drug interventions, and they can still remain ill, even profoundly disabled"*** (The CFIDS Chronicle Special Issue: The Science & Research of ME/CFS: 2005-2006:59)

- in 2007, the ME Association Medical Advisor pointed out that: "*Several research studies looking at prognosis have been published. Results from these studies indicate that ME/CFS often becomes a chronic and very disabling illness, with complete recovery only occurring in a small minority of cases. A recent Systematic Review of 14 studies found a median recovery rate of 7%"* (ME/CFS/PVFS: An exploration of the key clinical issues prepared for health professionals. Drs Charles Shepherd & Abhijit Chaudhuri, published by The ME Association, 2007).

(3) Whilst declining to carry out any subgrouping of "CFS/ME" (which would not accord with their intention to include as heterogeneous a population as possible), the PIs propose to carry out a secondary analysis of the data by using criteria that do not officially exist (the "London" criteria, which have been addressed above) as well as the CDC 1994 criteria (which also include psychiatric patients and do not specifically identify patients with discrete ME). If the PACE Trial entry criteria had been rigorously applied, no amount of secondary analysis would reveal those with discrete ME.

(4) The Investigators diluted the entry criteria after the PACE Trial had commenced by moving the SF-36 (physical function score) goalposts and by including people who had previously undergone CBT/GET. Originally, the SF-36 cut off point was set at 75 (Trial Identifier: 3.6) and those who had previously undertaken CBT/GET were excluded from the PACE Trial. However, on 9th February 2006 Peter White

wrote to the West Midlands MREC seeking permission to implement changes that had been set out on page 35 in the Full Protocol dated 1st February 2006 which had the specific aim of increasing recruitment (the SF-36 cut off point had been changed from 75 to 60 but was then changed again). Up to December 2005 (when the changes took place), the Investigators had excluded 65 people from 140 applicants. Thirty-six people had scored too highly on the SF-36 (so were deemed too well to take part in the Trial) and twenty-nine people had previously undertaken the treatment that was on offer in the PACE Trial (CBT/GET); thus 46.43% of 140 applicants had originally been rejected, but such people were then to be invited to take part.

Additionally, despite the Trial Identifier having stated at section 2.5 "*We will not recruit directly from primary care because we wish to compare the efficacy of these treatments in patients whom GPs regard as requiring additional help and who are likely to have a worse prognosis"*, in apparent desperation to reach their recruitment target, Peter White sought to advertise their trial to GPs, abandoning the protocol by which they intended to recruit "*consecutive new patients"* attending CFS clinics and seeking patients directly from primary care. In his letter, Peter White virtually begged GPs to send anyone who suffered from "*chronic fatigue (or a synonym)*" to a PACE Trial Centre. This means the Investigators are likely to have included people who are "tired all the time" (TATT), which bears no relationship to ME.

Furthermore, the Trial Identifier states at section 3.6: "*The RN* (research nurse) *will use a standard psychiatric interview…to exclude those with…a chronic somatisation disorder"*, but the Minutes of the Joint Meeting of the Trial Steering Committee and Data Monitoring and Ethics Committee held on 27th September 2004 record at point 12: "*Professor White noted that there were… changes already planned for (the Medical Screening Standard Operating Procedure [SOP]): Under medical history,* ***patients with hyperventilation or somatization disorder would not be excluded. The TSC were happy with this document.*** *Julia De Cesare to re-word the Medical Screening Standard Operating Procedure* ***according to Professor White's recommendations****"*. Clearly, therefore, Professor White recommended that people with somatisation disorder were to be included in the PACE Trial that purported to be studying those with "CFS/ME". The Trial Steering Committee and Ethics Committee apparently had no problem in agreeing to this further dilution of the trial cohort even though the trial was underway.

Deliberately to include those with known psychiatric disorder in a trial that purports to be studying those with a classified neurological disorder undermines the rules of scientific inquiry.

It cannot be denied that the PACE Trial Investigators changed the design of the Trial as they went along, which must surely undermine the reliability of all conclusions to be drawn from the data, not least because the first 75 participants recruited met different entry criteria from those who were recruited later.

This can only mean that, because the entry criteria had been diluted, people in the second tranche were less ill. It cannot be otherwise, even mindful that the Oxford criteria are wide enough to capture almost anyone (at the MERUK International Research Conference held on 25th May 2007 at the University of Edinburgh, Canadian psychiatrist Eleanor Stein said in her keynote lecture about the Oxford criteria that they: "*could describe almost anybody"*).

(5) The Investigators failed to take account of the extant literature about the disorder in question, which is a very serious issue in a clinical trial and is normally a pre-requisite.

(6) The Investigators mis-portrayed ME/CFS as a dysfunctional belief instead of a multi-system serious neuroimmune disorder.

(7) Even though they acknowledge they do not know what causes "CFS/ME", in the CBT and GET arms of the trial the PIs <u>assumed</u> that participants have no physical disease but did not inform participants of this and portrayed their own assumptions as established facts, which is misleading.

(8) The Investigators did not include essential pre-trial cardiovascular screening and specifically stated that if a participant suffered a stroke during the trial, such an event would not necessarily count as a Severe Adverse Reaction to treatment (Minutes of Trial Steering Committee meeting, 22nd April 2004, point 10).

(9) The Investigators chose a six minute walking test as "*an objective outcome measure of physical capacity*". According to the CMO's Working Group Report of 2002 (page 47): "*Perhaps the prime indicator of the condition is the way in which symptoms behave after activity is increased beyond what the patient can tolerate. Such activity, whether physical or mental, has a characteristically delayed impact, which may be felt later the same day, the next day, or even later…In some instances the person can sustain a level of activity for several weeks, but a cumulative impact is seen, with a setback after several weeks or more".* Moreover, the Chief Investigator himself, Peter White, has published evidence supporting the need for serial post-exercise testing -- see "Immunological changes after both exercise and activity in chronic fatigue syndrome: a pilot study". White PD, KE Nye, AJ Pinching et al. JCFS 2004:12 (2):51-66).

(10) The Investigators originally intended to obtain a non-invasive objective measure of outcome using post-treatment actigraphy but abandoned this on the grounds that wearing such a monitor would be too great a burden at the end of the trial (http://www.biomedcentral.com/1471-2377/7/6/comments). Therefore, after spending millions of pounds of public money and involving hundreds of people in an intensive regime, they completely fail to obtain objective measurements that would reveal whether or not the interventions are successful.

(11) The PACE Trial results will be based on participants' subjective responses to questionnaires. This is of particular concern when two of the interventions being tested (CBT and GET) specifically encourage participants to re-interpret their symptoms as not resulting from disease but as normal responses to exercise. Moreover, a study from 1997 demonstrated the problem of using self-reported data in ME/CFS patients (Vercoulen JH, Bazelmans E, Swanink CM, Fennis JF, Galama JM, Jongen PJ, Hommes O, Van der Meer JW, Bleijenberg G. Physical activity in chronic fatigue syndrome: assessment and its role in fatigue. J Psychiat Res. 1997 Nov-Dec; 31(6):661-73). The authors' reason for the study was because: "*It is not clear whether subjective accounts of physical activity level adequately reflect the actual level of physical activity….we evaluated whether physical activity level adequately can be assessed by self-report measures"*. The authors evaluated the correlations on seven outcome measures in relation to the actometer readings and demonstrated that "*none of the self-report questionnaires had strong correlations with the Actometer"*. Having evaluated whether physical activity level can be adequately assessed by self-report measures, the authors found that *"self-report questionnaires are no perfect parallel tests for the Actometer"* and that subjective questionnaires *"do not measure actual behaviour"* because "*responses may be biased by cognitions concerning illness and disability"*.

The authors continued: *"In earlier studies of our research group, actual motor activity has been recorded with an ankle-worn motion-sensing device (actometer) in conjunction with self-report measures of physical activity. The data of these studies suggest that self-report measures of activity reflect the patients' view about their physical activity and may have been biased by cognitions".*

There is thus evidence that alleged improvements reported in subjective questionnaires may not be reliable.

Furthermore, a study on (ME)CFS patients in the US by Friedberg et al that used CBT and which also encouraged activity found on actigraphy measurements that there was in fact a numerical decrease from the pre-treatment baseline (Cognitive-behaviour therapy in chronic fatigue syndrome: is improvement related to increased physical activity? J Clin Psychol 2009, Feburary 1).

(12) The PACE Trial Investigators did not disclose important information, for example, their own conviction that the participants do not have a physical disease, and their own assumption that two of the interventions, CBT and GET, do not work from a pathological perspective, only from a psychiatric perspective, **which could mean that participants were not in a position to provide fully informed consent.**

(13) The Investigators may have introduced bias by overtly favouring the CBT and GET arms of the trial by telling participants receiving these interventions that they can be curative, thereby invoking the placebo response and putting subtle pressure on those participants to report a positive outcome.

(14) The Investigators may not have achieved the required clinical equipoise of the trial because they have already formed their opinion that "CFS/ME" is psychogenic.

In clinical trials, there is an ethical requirement for equipoise, defined as *"the point where there is no preference between treatments, i.e. it is thought equally likely that treatment A or B will turn out to be superior"* (RJ Lilford et al. JRSM 1995:88:552-559). The Trial Protocol cites Lilford et al and moreover it states: *"those recruiting and randomising participants will rigorously maintain a position of equipoise and employ explanations that are consistent with this. All the participating clinicians regard all four treatments as potentially effective"*. However, it is evident that not all the participating clinicians believe all four treatments to be potentially effective, as the Manuals state that CBT and GET are potentially curative, whereas no similar claim is made for APT or SSMC. Furthermore, as stated above, Peter White and Trudie Chalder resigned from the CMO's Working Group Report because it supported the use of pacing. Is it ethical for the PIs to be responsible for a trial of pacing when they do not believe in it and even believe it has the potential to harm patients by maintaining them in a state of deconditioning and psychological dependency (ie. it "*may improve symptoms, <u>but at the expense of disability</u>*"—Trial Identifier Section 2.3).

Lilford et al are clear:

"Members of ethics committees should proceed on the basis that the question to be investigated has not already been answered. In some cases…the 'experts' (however defined) may all be in agreement as to which treatment is best. Under these circumstances the trial would be unethical.

"Just whose views are worthy of respect (and thus may be considered 'expert') may be a matter of some controversy…It cannot be assumed that (experts') strength of belief will always correspond to the strength of the evidence".

On this basis alone the PACE Trial seems to be unethical, because there is known agreement between the three PIs (and Wessely) that CBT and GET are superior to pacing (APT) and to SSMC.

Lilford et al further state:

"*…the public might become suspicious and resentful if clinicians fail to disclose personal preferences in the interest of…convincing other clinicians".*

Given the known and published views of the PIs and of Wessely, how can the PACE trial claim to have fulfilled the standard of equipoise described by Lilford et al and cited by the PIs when, from the outset, their own firmly-held views may have weighted the trial in favour of their preferred interventions?

In 1976, the current co-leader of the Oxford PACE Trial Centre, Professor Tim Peto, said about clinical equipoise:

"Physicians who are convinced that one treatment is better than another for a particular patient of theirs cannot ethically choose at random which treatment to give: they must do what they think best for the particular patient. For this reason, physicians who feel they already know the answer cannot enter their patients into a trial. If they think…that they know the answer before the trial starts, they should not enter any patients…" (Clinical Equipoise and RCT design. www.uab.edu/ethicscenter/weijer.ppt).

This, however, is precisely what the Principal Investigators are doing with the PACE Trial.

(15) The Investigators and some members of the Trial Steering Committee initially failed to declare significant financial conflicts of interest.

Because the PIs appear to have made very basic procedural errors, despite its cost and the involvement of the MRC that claims always to require rigorously high quality research (***"research excellence is always the primary consideration"*** -- letter from Simon Burden, MRC, 15th April 2005)**, can the results of the PACE Trial be scientifically robust?**

The results of the PACE Trial can do little for people with ME/CFS because the trial is based on a myth

ME/CFS is not "medically unexplained fatigue" perpetuated by aberrant illness beliefs, pervasive inactivity, membership of a self-help group, hypervigilance to normal bodily sensations and being in receipt of disability benefits.

The "CBT model" of CFS/ME is risible: why would countless successful professional people suddenly choose a life of financial deprivation, social isolation and unending stigma? It is a myth that they do so for the "gain" conveyed by the sick-role. Where is there any gain in being so sick, let alone a secondary gain?

It is disappointing that Action for ME was willing to be a party to a trial that, even before it began, the charity knew might make 50% of GET participants worse.

The cardinal concern about the whole PACE Trial must be that, whilst it nominally claims to have included people with ME/CFS, in reality it has intentionally included people with any form of "chronic fatigue", a reality supported by the advertisement placed by The Royal Free Hampstead NHS Trust for a research Cognitive Behaviour Therapist before the PACE Trial commenced. That advertisement stated: "*You will receive several months training prior to treating patients in the trial….You will be expected to…adhere closely to the treatment described in the therapy manual…This is a unique opportunity to…participate in a high profile Medical Research Council funded treatment for patients with* ***chronic medically unexplained fatigue (CFS/ME)***" (http://www.royalfree.org.uk/hrdocs/jobdocs/MS11008JD.PDF).

ME/CFS is a distinct, classified neurological disease, not a state of amorphous "Chronic Fatigue".

It seems that, now recruitment for the PACE Trial has finished, the Royal Free Fatigue Service Clinic is about to be closed. As recorded in Hansard (House of Lords) on 16th December 2009, the Countess of Mar asked Her Majesty's Government whether the Royal Free Fatigue Service has been instructed to return all CFS/ME patients to community mental health teams. Why are people with ME/CFS to be returned to community mental health teams? It is a myth that ME/CFS is a mental health problem.

Because it misrepresents the disease ME/CFS, the whole PACE Trial appears to be based on the myth that ME/CFS is a mental health disorder.

The PACE Trial literature (for which as Chief Investigator Peter White must bear ultimate responsibility) seems to be dismissive about doctors who do not agree with the "CBT model of CFS" (for example, the PACE Trial Newsletter number 3, December 2008, was dismissive about Dr John Chia's work demonstrating enteroviral infection in ME/CFS) and doctors who do not support the Wessely School model of "CFS/ME" seem to be portrayed as a problem, which may undermine patients' trust in doctors. To cast doubt on the judgment of other medical practitioners who do not subscribe to a particular view used to be in breach of the General Medical Council's Regulations (*"unsustainable comment which, whether directly or by implication, sets out to undermine trust in a professional colleague's knowledge or skills, is unethical":* GMC Professional Conduct and Discipline: Fitness to Practise, April 1992, Regulation 64). However, that clause has now been

amended. Indeed, Peter White actually included "Doctors" as a problem in his power point slides of his presentation at Bergen on 20th October 2009 in slide 37 in "Treatment issues" (http://www.meactionuk.org.uk/Bergen-Treatment-2009.pdf).

The myth that ME/CFS is a psycho-behavioural disorder has permeated the insurance industry to the extent that on 24th November 2009, a Senior Policy Manager at the Department of Health, Mrs Lorraine Jackson, wrote to Nick Starling, Director of General Insurance and Health at the Association of British Insurers:

"*I am writing about concerns that have been raised with Ministers and officials at the Department regarding the assessment of people with (CFS/ME) who are seeking payment of benefits under their insurance policies.*

"Patient groups suggest that the insurance sector is interpreting the clinical guideline published by the National Institute for Health and Clinical Excellence (NICE) on the diagnosis and management of CFS/ME, and particularly the outcome of the recent judicial review of this guidance, to mean that CFS/ME is a psychiatric rather than a physical illness. As a result, they claim that many insurance companies are opting out of making payments to people with CFS/ME where there is a psychiatric exclusion clause in the contract.

"The Department of Health accepts the World Health Organisation's (WHO) classification of CFS/ME as a neurological condition of unknown cause. The Department also accepts that CFS/ME is a genuine and disabling illness that can have a profound effect on those living with the condition.

"The purpose of this letter is to draw to your attention the very real anxieties that have been expressed by people with CFS/ME and those representing their interests".

That such a letter was deemed necessary demonstrates the very real and damaging effects of the Wessely School myth, for example, loss of benefits, loss of income protection and the consequent financial hardship that must be borne in addition to the burden imposed by the severity of the illness itself.

From the information received under the Freedom of Information Act, it seems that the MRC PACE Trial does nothing for those with ME/CFS. The reason is because the Wessely School's psychosocial model of "CFS/ME" does not accept the biomedical reality of ME/CFS: **the PACE Trial is intended to alter the way participants think about their disorder by re-structuring their thoughts and challenging their "negative thought patterns" by persuading them to believe that they are not sick, yet there is no research evidence to show that the many pathophysiological abnormalities that have been demonstrated in ME/CFS are caused by wrong beliefs or behaviour.**

There can be no comparison between the aim of the PACE Trial to alter participants' cognitions with supportive care for those coping with life-altering disease (as Wessely said: "***CBT is directive – it is not enough to be kind or supportive***", New Statesman, 1st May 2008) and the form of CBT used in the PACE Trial is indeed "directive".

As Michelle Strausbaugh noted (Co-Cure ACT: 7th September 2009), patients with multiple sclerosis feel no shame at being ill, and no fear that by admitting their disease – or even simply stating the name of the disease – they will immediately be labelled histrionic, lazy, and/or hypochondriacal which, perhaps because of the way they have been portrayed by the Wessely School's myth for the last two decades, is certainly the case for those with ME/CFS.

The Wessely School's myth -- that if basic tests are "normal", then the person must be somatising – has been comprehensively demolished by Professor Nancy Klimas and her team in the US. In a study looking at ME/CFS patients' total blood volume and at whether they had enough red blood cells, **Hurwitz and Klimas et al found that people with ME/CFS are likely to be anaemic despite "normal" test results**. This is because the standard blood tests for anaemia measure the number of red blood cells relative to the blood volume (Co-Cure RES 27th August 2009). However, as Klimas et al have demonstrated, patients with

ME/CFS have reduced blood volume, so as the total blood volume and the total red cells are both low, the results appear "normal", yet the patients may be functionally very anaemic. The study authors note: "*the elevated prevalence of low red blood cell volume suggests that the (ME)CFS subjects may have an anaemia type that goes undetected by standard haematological evaluations"* (Clin Sci (Lond) May 26, 2009; http://www.clinsci.org/).

The Wessely School, however, prefer to focus only on "normal" results, since if they conceded that there are measurable and reproducible abnormalities in ME/CFS patients, not only their psychosocial model of "CFS/ME" as a "functional somatic syndrome" but also their careers, their influential status as Government and insurance industry advisors and their reputations might be at risk.

Therefore, as Australian ME/CFS sufferer Susanna Agardy points out, rigorous diagnostic testing is being displaced by the "biopsychosocial" model in which the "bio" is usually ignored -- Wessely School psychiatrists insist that certain physical symptoms must be psychogenic: "***Their insistence on their confined terms of reference is breathtaking. They tend to go round and round finding confirmation of their beliefs without ever examining whether their whole paradigm might be out of touch with reality. Apparently living in a separate bubble of their own making, they ignore all evidence which might contradict their position…money is spent on researching 'biopsychosocial' explanations which are facile, simplistic and mostly make the wrong assumptions***" (Co-Cure ACT: 4th August 2009).

Despite the extensive evidence-base that ME/CFS is a serious multi-system organic disease, the anticipated impact of the PACE Trial which recruited participants on the basis of broad "fatigue" is that the findings will be used to justify the continued use of behavioural interventions in clinical practice throughout the UK -- and probably internationally -- for people with ME/CFS.

There may, however, be a glimmer of hope: at the MRC Workshop on CFS/ME held on 19th / 20th November 2009 at Heythrop Park, Oxfordshire, in his introduction Professor Stephen Holgate said, in effect, that the reason for the meeting was the need to move forward, **to get away from old models and to use proper science**, and that there was no reason not to change things, a view he had also expressed at the RSM meeting "Medicine and me" on 11th July 2009.

The question is -- will the results of the MRC PACE Trial and the vested interests of the Wessely School ever permit the getting away from *"old models"*?

On 15th December 2009 the Daily Mail reported the words of Sir Ken Macdonnell QC, a former Director of Public Prosecutions: "***Self-belief is no answer to misjudgment***". Those words were said of former Prime Minister Tony Blair about his decision to go to war in Iraq on the basis of no actual evidence of weapons of mass destruction (WMD).

Could they equally apply to the apparent self-belief and misjudgment of the PACE Trial Investigators about ME/CFS?

In an article on 2nd November 2004 entitled "M.E. and Political Conflict", William Baylis wrote:

"Though it is nominally a research trial into M.E., the Medical Research Council's current 'PACE' trial has been very cleverly designed to exclude most true M.E. sufferers and include sufferers of mental illness. ***As such, the trial is a deceitful national scandal and a gross abuse of tax payers' money.*** *When the skewed results of this trial begin to be used by Government, the NHS and the DWP, M.E. sufferers should be under no illusions as to what it will mean. They will face forced and increasing physical exercise programmes at the hands of psychiatrists in the twelve new regional 'M.E. Treatment Centres'. Patients' negative responses to such programmes will be viewed by these psychiatrists as evidence of mental illness – thereby presenting an appalling no-win situation to physically vulnerable people. There is now much international research evidence demonstrating why patients with M.E. (ICD-10 G93.3) will respond negatively…However, these Wessely School psychiatrists ignore such hard evidence because they are working to their own corporate-backed agenda. In opposition to good science they simply assert that M.E. is not a real*

physical illness and is only an 'aberrant belief'…The well-intentioned but wholly misplaced attempt to dialogue with and influence these corporate-backed psychiatrists has not only failed to secure progress, it has led to the extremely dangerous situation now at hand…I would solemnly caution the M.E. community to beware of people attempting to persuade us not to confront…corporate-backed psychiatrists…These people are not open to reason, they are the enemy of good science and the enemy of M.E. sufferers…The time has come to sadly disassociate with MEA, AfME and other appeasers – they are part of the problem, not the solution…The one thing we have on our side is that Wesselyites do not is science. It is time to expose bad science and vested interest" (http://wp.me/p7FYk-3a).

As one severely affected ME sufferer wrote: "*When they publish the PACE 'results' there will be widespread suffering on a scale hitherto unknown"* (letter to Heather Walker at AfME, 8th June 2007). The correspondent continued: "*We've had enough of the damage the IoP and Barts and their supporters have wreaked locally via GPs, and the endless continuous stress we are subjected to by their influence on the DWP – never mind the research environment, which they have managed to devastate over the years…None of this has happened mysteriously. Individuals are responsible, and they tend to have names".*

Disturbingly, perhaps as a result of the Wessely School myth, the on-going disdain and contempt in which extremely sick ME/CFS sufferers continue to be held is reflected by contributors to "Advances in Psychiatric Treatment" 2010:16:1:doi:10.1192/apt.16.1.1. Discussing the forthcoming revision and harmonisation of the two major classifications ICD and DSM, the Editor, Joe Bouch, states:

"*Sartorius gives a behind-the-scenes view of the revision process.* ***There are many vested interests: not just clinicians, but governments, NGOs, lawyers, researchers, public health practitioners, Big Pharma and patient groups. Vast sums are at stake*** *– everything from welfare benefits and compensation claims to research budgets…****Like Sartorius, Thornicroft singles out chronic fatigue syndrome, 'bitterly contested in terms of its status as a physical, psychiatric or psychosomatic condition' and viewed by healthcare staff as a 'less deserving' category".***

Referring to ICD-10, Sartorius (to whose 1990 book "Psychological Disorders in General Medical Settings" Wessely contributed the chapter "Chronic Fatigue and Myalgia Syndromes": see Section 1 above) himself states: "*Some of the categories that one would expect to find in a chapter devoted to mental disorders have been placed elsewhere, mainly because of pressures exerted by those who did not want to be labelled by any particular 'psychiatric' diagnosis. Thus, for example, chronic fatigue syndrome, which was listed together with neurasthenia for a long time, is now in the chapter containing infectious diseases which are supposed to be causing it".* This is remarkable for three reasons, first because ICD-10 G93.3 is contained in Chapter 6 under Disorders of the Brain (not under Infectious Diseases); secondly because ME (for which CFS is a synonym) has never been classified in the ICD as neurasthenia and thirdly, Norman Sartorius is President of the Association for the Improvement of Mental Health Programmes and holds professorial appointments at the Universities of London, Prague and Zagreb and at several other universities in the USA and China. He was a member of the WHO's Topic Advisory Group for ICD–11 and a consultant to the American Psychiatric Research Institute, which supports the work on the DSM–V. He has also served as Director of the Division of Mental Health of the WHO and he is a past President of the World Psychiatric Association and of the Association of European Psychiatrists, so one could expect him to be accurate.

Without the correct application of the scientific process, there can be no advancement of knowledge. There should be open debate and discussion, not suppression or dismissal of evidence that does not support a particular theory.

The FINE Trial results do not support the Wessely School's model, but contrary to the most basic principal of science, the Wessely School remain wedded to a theory that is not supported even by their own evidence.

Notwithstanding the FINE Trial results, it is widely expected that the PACE Trial results will support the Wessely School's model of "CFS/ME" not least because, according to Professor Peter White, the aim of the

PACE Trial is about *"Health economics and societal costs"* (Bergen, October 2009) and people with ME/CFS currently cost the State a great deal of money.

The current edition of the General Medical Council's "Good Medical Practice" requires that every registered medical practitioner must *"Keep your professional knowledge and skills up to date"* (http://www.gmc-uk.org/guidance/good_medical_practice/duties_of_a_doctor.asp).

To reiterate: **since the general body of knowledge known about by other clinicians and researchers working in the field of ME/CFS is now so great, the question repeatedly asked is: at what point will that body of scientific knowledge be so great that it will be considered serious professional misconduct to ignore it and to continue to deceive patients by pretending that it does not exist?**

On 27th January 2010, The Independent carried a feature on ME in which Jane Colby, Executive Director of The TYMES Trust, said: "***Unfortunately, we are in a situation where professionals in medicine, education and social services still do not know how to recognise it and where its terrible severity goes unrecognised***". One of the Trust's young members was quoted as saying: *"Doctors appear uncomfortable with the entire subject and are often dismissive and judgmental. It's completely isolating… even family members get tired of hearing how utterly ill and bone weary you feel… They say you have good days and bad days; you don't: with ME, you have bad days and worse days mostly. You get tired of always feeling ill and not being able to do anything".*

Nine years ago, the ME Association's Medical & Welfare Bulletin carried an item about doctors' attitude to patients with ME/CFS: referring to a previous article in the April 2000 issue of Medical Matters about the same problem, the MEA Medical Advisor, Dr Charles Shepherd, wrote:

"Problems with rude, hostile or disbelieving doctors brought in one of the largest responses of the year. Unfortunately, it seems that when a formal complaint has been made about unacceptable professional behaviour, it becomes extremely difficult to get anyone in authority – even the General Medical Council – to take the matter seriously. Even so, I still think that people should make a complaint where a doctor's attitude has clearly been objectionable or prejudicial to good clinical care" (MEA Medical & Welfare Bulletin, Issue 2, 2001, page 17).

In 2010, little seems to have changed for the better for the hapless ME/CFS patient in the UK and the Wessely School myth seems to be alive and well, as evidenced by two registered medical practitioners' published views about patients with the disorder.

Far from being "*the militant ME brigade*" as described by "Dr Crippen" (Guardian, 3rd Feburary 2010) **or the "*the Terrorists of Health in full jihadist mode*" as alleged by Dr Mark Borigini** (Psychology Today; 20th January 2010)**, people with ME/CFS are immensely courageous; they do, however, seek to dispel once and for all the Wessely School myth that ME/CFS is a mental disorder and they seek urgent change in the perception of ME/CFS in the UK.**

They must now take heart from the message of the President of the International CFS/ME Association, Dr Fred Friedberg, about the removal of Dr William Reeves from his post as head of (ME)CFS at the Centres for Disease Control in the US:

"I believe that the leadership change effort of the IACFS/ME over the past several months was critical to this successful outcome. In particular, strong and compelling testimony from a number of high profile (ME)CFS professionals…played an important role in publicly airing the long-standing problems with the CDC (ME/CFS) programme. The success of this effort shows that the (ME)CFS community can help to shape and move forward the scientific agenda that confers to (ME)CFS the recognition that it truly deserves" (3rd February 2010: http://www.iacfsme.org/ : Co-Cure NOT: 4th February 2010).

Many people believe that there is the same pressing need for the removal of those currently in charge of the ME/CFS programme in the UK because, as Professor Holgate affirmed, it is time to get away from old models and to use proper science.

This need is supported by patients who posted messages on the ME Association's Facebook site (spelling and syntax adjusted for clarity):

Post # 1, 30th January 2010: *"The MRC are supposedly trying to help sufferers of CFS/ME so why is Prof White on this panel; he is a very bad seed. I have never met a single patient who has a good word to say about him and never met anyone who has been cured by his 'treatment'. He just doesn't deserve to be there…he also helped set up the Frenchay CFS/ME service in Bristol which is the most awful place I have ever had the misfortune to end up in; not only did they not help, they made my health situation a lot worse".*

Post # 2, 30th January 2010: *"I had the misfortune of attending Bart's CFS Clinic headed by Prof White and I never returned after the first visit. They tried very forcefully to get me to try GET even after explaining how severely affected I am and how hard it was for me to attend Bart's…How Prof White can advise the DWP while he works for a medical insurance company is beyond comprehension. If that is not a conflict of interest, then what is?".*

Post # 4, 30th January 2010: "*Prof White is, I'm sure, very happy with the way the MRC is funding research: as well as giving millions to fund the PACE Trial, they have also funded other projects headed by Charlotte Clark and Kam Bhui in the institute he (PDW) is involved with, while the MRC has not been funding research projects which might challenge his views. So he will be happy with the status quo while most people including Prof Holgate think the MRC needs to change with regard to ME and CFS and the grants they are funding.* ***I think it would be good if all the people on any committee knew where Peter White was coming from***"
(http://www.facebook.com//group.php?v=feed&story_fbid=226500923256&gid=68630803256#/topic.php?uid=68630803256&topic=12993).

Indeed so.

As Nobel laureate Professor Richard Feynman famously said about the nature of the scientific process: "*First you guess…Then you compute the consequences. Compare the consequences to the experience.* ***If it disagrees with the experience, then the guess is wrong.*** *In that simple statement is the key to science. It doesn't matter how beautiful your guess is…If it disagrees with experience, it's wrong. That's all there is to it*" (http://www.staticearth.net/copern.htm).

As demonstrated, the Wessely School not only ignore the biomedical evidence that ME/CFS is not a behavioural disorder, they also ignore their own evidence that their preferred interventions are not successful; can they therefore be said to be practising science or blindly following an ideology?

APPENDIX I: Dr Tony Johnson, Deputy Director of the MRC Biostatistical Unit, Cambridge

The UK ME/CFS community noted with some surprise the involvement of Dr Tony Johnson in the PACE Trial because his published views on psychiatric trials are already known. In 1998 he published a major review entitled "Clinical trials in psychiatry: background and statistical perspective" (Statistical Methods in Medical Research 1998:7:209-234) in which he noted the existence of studies produced by psychiatrists that claim *"inordinate enthusiasm"* for certain therapies.

Dr Tony Johnson is the son-in-law of Dr Elizabeth Dowsett, who was formerly Medical Advisor to and President of the ME Association. Correspondence exists between an ME/CFS sufferer and Dr Johnson himself, but which also involves Dr Anthony C Peatfield, Head of MRC Corporate Governance and Policy.

The correspondence arose from Johnson's Quinquennial Report for the MRC's Biostatistical Unit's progress report for the years 2001 to 2006 that was placed on the website of the MRC Biostatistics Unit (BSU).

Taken from the BSU's Quinquennial Review of 2006, one part of which 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; under "Chronic Fatigue Syndrome (CFS), with P White, T Chalder (London), M Sharpe (Edinburgh)", 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. In response to a DH (Department of Health) Directive, MRC called for grant proposals for investigations into CFS as a result of which two RCTs (PACE and FINE) were funded and have started despite active campaigns to halt them. I am part of the PACE study, a multi-centre study comparing cognitive behaviour therapy, graded exercise training, and pacing in addition to standardised specialist medical care (SSMC), with SSMC alone in 600 patients. I have been fully engaged in providing advice about design of PACE and I am a member of both Trial Management Group and Trial Steering Committee. I am not a PI (Principal Investigator) because of familial involvement with one of the charities, a perspective that has enabled me to play a vital role in ensuring that all involved in the PACE trial maintain absolute neutrality to all trial treatments in presentation, documentation and assessment".*

Johnson's Report on "CFS" research rang alarm bells within the ME/CFS community, since it openly stated that he, personally, had a *"vital"* role to play in ensuring what ought to have been taken for granted in any MRC trial, namely the *"absolute neutrality"* of the PACE trial.

Upon seeing this on the MRC Biostatistics Unit's (BSU) website, an ME/CFS sufferer wrote first to 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.

There was no acknowledgement from either the MRC BSU or from Dr Johnson; however just after the letters had been sent to the MRC, it was observed that much of Dr Johnson's Report had been removed from the MRC BSU website, indicating that this was a matter of some importance to the MRC.

In statistical terms, the deletions from Dr Johnson's Report amounted to a substantial 42% of the entire Report.

Almost a full month later, a letter dated 10th October 2006 was received from Dr Anthony Peatfield, which said: *"You refer to some text that was recently published on the website of the MRC Biostatistics Unit. The comments to which you refer were drawn from a progress report produced by an individual member of staff.* ***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. While the comments were ill-judged, it was not the intention of the individual who wrote them, nor the Unit in publishing them, to cause offence".*

Curiously, Dr Peatfield further advised that should anyone else contact the MRC about this same matter: *"we shall reply to any further requests such as your own as indicated in the third paragraph, above*", meaning that he would simply offer an 'apology' regardless of what information or clarification was being requested.

Peatfield's reply implied that those damaging comments were not made by anyone of significance at the MRC, when in fact they had been written by the Deputy Director of the MRC Biostatistics Unit who was intrinsically involved with the actual design of the PACE trial, namely Dr Tony Johnson.

Out of ten Reports that constituted the Quinquennial Review, the only individual report from which sections were removed, including the Abstract, is that of Dr Johnson.

The Abstract could not, however, be removed from the Review Index, where all ten Abstracts by different individuals are located, with links to their full documents. In the case of Dr Johnson's "re-edited" document, the link to the Abstract no longer works, but the link works for all the other Abstracts. Was this a ploy by the MRC to conceal Johnson's Abstract, with its references to his close association with the Institute of Psychiatry?

Amongst large amounts of text removed from Dr Johnson's Report were details of exactly how influential Dr Johnson has been within the MRC and with the Institute of Psychiatry, particularly in terms of securing MRC funding, along with other details of his close connections to key individuals involved in the PACE trial. The following extracts are taken from the Abstract, which was removed in its entirety from the body of Dr Johnson's Report:

"Abstract

"I have initiated, developed, and collaborated in both clinical trials and epidemiological studies in four challenging medical specialties working with a large number of collaborators geographically dispersed throughout UK, Europe, and beyond. These have resulted in major advances in the understanding of the efficacy of cognitive therapy.

"Over many years my programme has contributed to the successful completion of the three largest clinical trials, all of major international importance. My programme will be exploited in the future in further collaborations with the pharmaceutical industry.

"I have enabled a successful collaboration linking the research programmes of this Unit with the MRC Clinical Trials Unit (MRC CTU) in London, that has resulted in the establishment of a new Clinical Trials Unit dedicated to mental health and neurological sciences at the Institute of Psychiatry in London. The linkage has enabled my expertise in clinical trials to be extended to chronic fatigue syndrome and the setting-up of a major MRC study to evaluate the efficacy of four different interventions.

"I have advised many clinical trialists on the setting-up of organisational structures including Steering and Data Monitoring Committees, and Management Groups".

Some of Dr Johnson's credentials, however, remained on the MRC BSU website: *"I present my eighth and final Unit review report since joining MRC Neuropsychiatric Research Unit in 1968; a period exceeding 37 years during which I have been very privileged to engage fully in the research programmes of MRC, be a co-editor for 18 years of the first major journal in medical statistics (Statistics in Medicine), found an international society (Society of Pharmaceutical Medicine), draft the Constitution for another (International Society for Clinical Biostatistics), and contribute to UK Government, European, and International working parties and committees.*

"In view of my retirement in September 2008 I describe only my research programme over the past five years without reference to the future". The following text was removed: *"but note that none of my projects will terminate in the near future, for they will be continued and expanded by others, many of whom I have trained for that purpose. My role within MRC changed radically in 2001, resulting in my switching from independent band 2 to core scientist.* ***My expertise in clinical trials was needed to expand the activities of the Department Without Portfolio into areas such as mental health (and) chronic fatigue, currently the focus of government health policy".***

From the above, it can be seen that Dr Johnson was an influential figure in the MRC BSU and, as Deputy Director, his in-house review was a substantial document. For the MRC Head of Corporate Governance and Policy (Dr Anthony Peatfield) to have referred to Johnson as a mere *"member of staff"* and to imply that the comments in question were not connected to anyone of significance at the MRC seems to indicate an intention to avoid accountability and to purposefully mislead the public. Johnson's Report was an important official communication from one professional to others. **Coming from such a senior figure within the MRC, and considering his level of involvement with the PACE trials, Johnson's adverse comments about CFS would have carried considerable authority and influence.**

Moreover, it seems that Dr Johnson may have been advising the Wessely School psychiatrists how best to obtain MRC funding from the advantage of his influential and knowledgeable position as a core MRC scientist through the close links he had forged with the Institute of Psychiatry.

Disturbingly, it seems that in his material which was removed from the MRC website, Johnson revealed that he had used data (which he described as a *"perspective"* that he had been able to obtain through *"familial involvement with one of the charities"*) to assist in the design of the PACE trial. If this is so, what is he implying? **The PACE trial is about challenging ME/CFS sufferers' beliefs: is Johnson somehow using the *"perspective"* he has obtained through *"familial involvement with one of the charities"* to design a trial whose aim is to promote a management regime that has already caused so much harm to members of that charity?**

Most disturbingly of all, as mentioned above, Johnson stated that he was playing a *"vital"* role in maintaining *"absolute neutrality"* by *"all involved in the PACE trial"*. This clearly indicates that Johnson believed that without his own *"vital"* role, *"absolute neutrality"* would <u>not</u> be achieved.

The word "vital" means "essential", so was Johnson effectively conceding that he knew the PACE trial was fundamentally biased but that he – as an individual -- was dealing with the people involved in the trial who are known to be intent on dismissing "ME" and on promoting their own beliefs about the use of CBT/GET for those with "CFS"? Why is it only his own *"vital"* role that will ensure the *"neutrality"* of the PACE trial?

Having taken seven months to reply to a letter that had been sent to him personally, on 7th November 2006 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"*.

Having earlier informed colleagues in his Report that: "*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*", Dr Johnson 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".*

Also in his letter of 7th November 2006, Dr Johnson simultaneously did "*not know when CFS/ME became controversial or why*" but nevertheless proffered his speculation that *"controversy sometimes arises when the evidence base is slender as many views and ideas can be put forward without any means of resolving them. The publication of a large number of research papers in the medical literature, some of poor quality or based on small samples only leads to further confusion".*

This is an interesting piece of conjecture, given that the post of Statistician Clinical Trials Unit (CTU) Division of Psychological Medicine Ref No: 06/A09 is described as the "Johnson_Wessely_Job" (07/07/2006) at The Institute of Psychiatry where: "*The team works under the direction of Professor Simon Wessely, the Unit Director. The team is supported by the regular input of a Unit Management Group from within the Institute of Psychiatry. The statisticians within the Unit also have regular supervision meetings with Dr Tony Johnson from the MRC Clinical Trials Unit. The post holder will be directly responsible to the CTU Manager (Caroline Murphy), supervised by the CTU Statistician (Rebecca Walwyn) and will be under the overall direction of the Head of Department, Professor Simon Wessely".*

As no satisfactory response had been received to a perfectly valid request for further clarification (ie. the names of individuals involved with the PACE trial who, Johnson believed, would, without his own *"vital"* intervention, be unable to maintain the requisite "*neutrality*" which he was able to ensure through his "*familial involvement*" with one of the charities), the ME/CFS sufferer wrote again with the same request.

Over five months after that request, Dr Johnson sent a further letter dated 2nd April 2007 in which he wrote: "*The issues that you raise here are complicated. First it is important to realise that there is a substantial range of opinion among clinicians about the relative merits of some treatments".*

Johnson's reply was a five-page masterpiece of confabulation but still did not answer the question asked. Instead, amongst other diversions, he wrote at length about SSMC (standardised specialist medical care) for those with ME/CFS as part of the PACE trial, causing another ME/CFS sufferer to ask:

"What is the accepted definition of standardised specialist medical care (SSMC) for those with ME/CFS? In order to achieve an accurate assessment of the PACE trial outcomes, there must be a definition of standardised specialist medical care, so what is this definition and where is it accessible? (It is a matter of record that there isn't one). Tony Johnson accepts that an early design for the current PACE trial did not include an SSMC group but he seems to have expediently overlooked the reality that there is **no** *SSMC for those with ME/CFS, as Catherine Rye made plain in 1996 about the Sharpe et al paper of the Oxford trial of CBT/GET: 'I am a sufferer and participated in the Oxford trial. There are facts about the trial that throw into doubt how successful it is. It is stated that patients in the control group received standard medical care. I was in that group but I received nothing' "* (Independent, 30th March 1996, page 16).

The same ME/CFS sufferer also asked:

"*What is Tony Johnson's statistical rationale for deliberately mixing patient cohorts in the PACE trial? Against the evidence that mixing study populations is inadvisable, the PACE trial is mixing at least three different groups of patients.*

"Fibromyalgia patients are included in the Principal Investigator's own selection of those with "CFS/ME" for the MRC PACE trial, as well as those with other states of chronic fatigue, including psychiatric states, yet all three categories are taxonomically different and are classified differently by the WHO.

Fibromyalgia is classified at ICD-10 M79.0; ME/CFS is classified at ICD-10 G93.3 and other fatigue states are classified at ICD-10 F48.0.

"In a reply dated 15th April 2005 to Neil Brown, Simon Burden of the MRC wrote: 'When researchers put together a proposal they are required to define the population they are studying'. Why does this basic requirement not apply to the PACE trial and how will the outright abandonment of this MRC principle affect Johnson's statistical analysis of the PACE trial?

"How does this accord with what Simon Burden asserted was the MRC's requirement for 'the high scientific standard required for funding'?

"Johnson acknowledges in his reply (on page 4) that: 'It is important to realise that there is a substantial range of opinion among clinicians about the relative merits of some treatments'. Indeed, this is so. What, then, is his statistical explanation for the MRC's undue reliance on the ill-founded beliefs of Wessely School psychiatrists, given the large body of undisputed published evidence that their beliefs about the nature of ME/CFS are simply wrong? Johnson states in his reply: 'in designing the trial we had to guess the outcomes and our guesses (were) mostly based on published studies". For what statistical reasons did the MRC rely on Wessely School studies, when there is abundant published criticism of those very studies and their flawed methodology in the literature?

"Throughout his reply, Johnson uses the terms: 'In designing a clinical trial (of CBT/GET) we have to estimate the number of patients'; 'Estimation essentially requires a guess at what the results will be'; 'In guessing what the results may be…'; 'The assumptions we make…'; 'Broadly, we assumed that around 60% of patients in the CBT group would have a 'positive outcome' at one year follow-up….'; 'We speculated that….', ***so there is now written confirmation from the MRC Biostatistics Unit that the whole PACE trial is based on guessing, speculation and assumption. Would Tony Johnson explain how this accords with the MRC's supposed requirement for high standards?".***

It was suggested that Johnson be asked to explain how statistics had suddenly become a matter of guesswork, speculation and assumption.

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 and the 25% ME Group for the Severely Affected) that were calling for the PACE trial to be halted.

As noted above, from this whole episode concerning Dr Johnson's Report, the ME/CFS 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 that the seam of Wessely School dismissal and denigration does indeed run deep.

APPENDIX II: Response to Dr Gabrielle Murphy (Royal Free Hospital Fatigue Service)

"Coercion as Cure?"

authors' response to allegations of defamation made by Royal Free Hampstead NHS Trust concerning the Fatigue Clinic

Eileen Marshall Margaret Williams 30th November 2007

1. It is noted that in all her references to our article, Katina Shand (Claims Manager, Risk and Safety Department, The Royal Free Hampstead NHS Trust) has converted the title of our document from a question to a statement by the omission of the question mark that was an integral part of the title. In law, the asking of a question does not constitute defamation.

2. In her email of 30th November 2007 (sent at 10.41am), Katina Shand stated: "*I have contacted Dr Gabrielle Murphy to ask for her comments regarding the contact of the article 'Coercion as Cure' and I have attached her response*". Does Ms Shand mean to say "*content of the article*"?

3. We note that it was only following her original email of 26th November 2007 (sent at 2.27pm) that Katina Shand sought comments upon our article from Dr Gabrielle Murphy. We had understood from Ms Shand's original email that prior to contacting us, Royal Free Hampstead NHS Trust staff had already alleged that "*several statements*" in our article were "*defamatory towards both the trust and it's* (sic) *staff*".

4. It is noted that in her Statement, which was undated and unsigned, Dr Gabrielle Murphy categorically asserts that it is not, and never has been, the policy of the Fatigue Service at the Royal Free Hospital to deny access to the specialist physician "*for assessment or re-assessment*". That is not what we asked in our email to Ms Shand of 26th November 2007 sent at 19.04, nor what we said in our article: we specifically asked if it was, or ever had been, the policy of the Fatigue Clinic that access to a physician would not be granted (except on admission or discharge from the Fatigue Clinic) unless a patient agreed to participate in CBT/GET. The issue does not therefore relate to "*assessment or re-assessment*": the issue relates to whether or not a patient attending the Fatigue Clinic would have access to a physician (as distinct from a physiotherapist or an occupational therapist or a psychotherapist) about any aspect of their medical care unless they had agreed to participate in CBT/GET.

5. However, in her paragraph 5, Dr Gabrielle Murphy herself concedes that (quote): "*patients who are not having one of the therapies in the Fatigue Service are discharged to the care of their GP*". How does this differ from what we said in our article (*"patients will have access to a physician for medical advice at the Centre only if they agree to participate in CBT and graded exercise therapy regimes; if patients decline to enter into a contract to participate in such regimes, they will have no access to a physician at the Centre"*)? As Dr Murphy has conceded that patients who are not having one of the therapies offered by the Fatigue Service will be discharged from the Fatigue Service, we fail to see how our statement can be deemed by either Dr Murphy or by the Royal Free Hampstead NHS Trust to be defamatory.

6. Since Dr Murphy has conceded that what we wrote is true, we maintain that our subsequent statement likewise cannot be considered defamatory because it is accurate: *("Less than one month after publication of the NICE Guideline on "CFS/ME" on 22nd August 2007, the Royal Free Fatigue Service Centre policy which refuses and denies patients access to a physician unless they agree to be coerced into taking part in a regime that is already known to be harmful in 50% of participants is in blatant breach of that national Guideline").* Since Dr Murphy concedes that *"patients who are not having one of the therapies in the Fatigue Service are discharged"*, this effectively means that patients attending the Royal Free Hampstead NHS Trust Fatigue Service

who do not agree to take part in CBT/GET have no access to a physician at the Fatigue Service, which is what we said in our article.

7. In this respect, we draw attention to what we said in our article, namely that the Parliamentary Under Secretary of State, Lord McKenzie of Luton, said on 28th February 2007 (reported in Hansard: GC198): "*There is no requirement for individuals to carry out any specific type of activity or treatment. That cannot be sanctioned*".

8. Our article pointed out that the NICE Guideline on "CFS/ME" specifically states in ten different places that access to a physician must not be dependent upon patients agreeing to participate in a CBT/GET regime and that refusal to take part in such a regime should not end treatment contact with the doctor. Indeed, the Guideline stipulates that such patients **may not be discharged from medical care** (see the Full Guideline pp 28, 31, 116, 130, 158, 178, 214, 259, 283 and 298). As Dr Gabrielle Murphy herself states, patients attending the Royal Free Hampstead NHS Trust Fatigue Service who decline to take part in a CBT/GET regime are being discharged from medical care, which is contrary to the NICE Guideline. We do not see how, by stating that "*patients who are not having one of the therapies in the Fatigue Service are discharged*" (as confirmed by Dr Murphy herself), our article was defamatory in this respect.

9. It is noted that Dr Murphy states that the RFH has been recruiting patients for the PACE trial since October 2006, and that of some 750 patients seen since then, 68 have been recruited. We note that this represents 9.1% of patients seen. From the information provided by Dr Murphy, it is unclear what "*different therapies*" are being offered to 334 patients out of the 750 attending the Fatigue Service.

10. The evidence that 50% of patients with ME/CFS are known to have been harmed by CBT/GET comes from four major surveys: (i) Action for ME; (ii) a combined report for the ME Association and AfME carried out by Dr Lesley Cooper; (iii) the report of the 25% ME Group for the Severely Affected and (iv) the report of DM Jones MSc. All are in the public domain.

11. In relation to the DLA forms, it is within our knowledge and belief that not all patients attending the Royal Free Hampstead NHS Trust Fatigue Service were made aware that (quoting Dr Murphy): "*this is indeed a proforma paragraph but it is always followed up by details specific to the patient*". It is within our knowledge and belief that some patients understood only that the Fatigue Service no longer signs individual applications for DLA, which is what we said in our article ("*It has also been established that this same Centre is no longer prepared to support individual patients' applications for Disabled Living Allowance but simply hands patients a pro-forma letter")*. It is noted that Dr Murphy concedes that a pro-forma does exist. It is our understanding that the fact that such a pro-forma is "*always followed by details specific to the patient*" has not been made clear to some patients, who we understand were told that: "*We don't do individual reports for DLA any more*".

12. In her original communication of 26th November 2007 at 2.27pm, Katina Shand alleged that: "*there are several statements that are defamatory towards both the trust and it's* (sic) *staff*". In relation to Dr Gabrielle Murphy, we made no mention of her by name apart from pointing out what is already in the public domain, namely that she is part-time Clinical Lead at the Fatigue Services Centre. In relation to other members of staff, we point out that what we said about Nathan Butler (a graded exercise therapist) and about Karen Levy (an occupational therapist) were taken from the Royal Free Hampstead NHS Trust's own website. This was posted on 16th October 2006 (see: http://www.royalfree.org.uk/default.aspx?top_nav_id=2&tab_id=15&news_id=326).

13. We also point out that what we said about Professor Peter White in relation to the Royal Free Hampstead NHS Trust Fatigue Service ("*In the absence of the part-time Clinical Lead at the Royal Free Fatigue Service Centre, Dr Gabrielle Murphy, the person in overall charge is Professor Peter White")* also comes from the Royal Free Hampstead NHS Trust website. It comes from a job advertisement that was created and modified by Rachel Buchanan on 30th August 2007

(at 15.46 hours). We note that whilst other job advertisements dating back to 2004 are still on the Trust's website, that particular one seems to have been removed. We confirm that not only do we ourselves have both electronic and hard copies, but that numerous other people also have copies and are aware of Professor White's involvement with the Trust's Fatigue Service.

We wish to make plain that if it can be unequivocally demonstrated that we have made defamatory statements about the Royal Free Hampstead NHS Trust or any of its staff members in our article, then the relevant sentences will be removed from the article on the website http://www.meactionuk.org.uk and an explanation, full retraction and public apology will be posted on that same website. In this event, in the interests of transparency, this correspondence will also be posted on the same website.

Appendix III: Dr Melvin Ramsay's description of ME that was approved by the West Midlands MREC

Dr Melvin Ramsay's description of myalgic encephalomyelitis

Please score whether you have had any of the following symptoms in the last week:

Score each symptom by putting a circle round the number that most closely resembles the frequency and intensity of that particular symptom.

0 = not at all present
1 = present a little, and mildly
2 = present more often than not, and moderately
3 = present most of the time, and quite severe
4 = present all the time, severely

Symptom:					
Fluctuation of symptoms from day to day or within the day	0	1	2	3	4
Headaches	0	1	2	3	4
Giddiness	0	1	2	3	4
Muscle pain	0	1	2	3	4
Muscle cramps	0	1	2	3	4
Muscle twitchings	0	1	2	3	4
Muscle tenderness	0	1	2	3	4
Muscle weakness	0	1	2	3	4
Pins and needles	0	1	2	3	4
Frequency of passing water	0	1	2	3	4
Blurred vision	0	1	2	3	4
Double vision	0	1	2	3	4
Increased sensitivity of hearing	0	1	2	3	4
Increased sensitivity to noise	0	1	2	3	4
Ringing in your ears (tinnitus)	0	1	2	3	4
"Feeling generally awful"	0	1	2	3	4
Muscle weakness after exercise	0	1	2	3	4

Appendix IV: the advent of UNUMProvident into the UK benefits system

For a company that was hired to work within a UK Department of State, UNUMProvident has an interesting track record and a reputation that continues to date:

- After the 1993 Budget, Peter Lilley, then Social Services Secretary, hired the Vice President of UNUM private insurance company to help in his bid to save £2 billion per year by slashing the benefits for disabled people

- Crucial to the new UK disability rules were tougher medical tests. To this end, new tests were introduced that were fundamental to the savings Peter Lilley hoped for. To implement the tougher new tests, Lilley's Department set up a "medical evaluation group" for which they recruited a new corps of doctors; the most famous member of that group was Dr John Lo Cascio (Vice President of the UNUM Corporation), who was seconded to the company's British arm based in Dorking, Surrey

- Lo Cascio was invited by Lilley's Department to help in the extensive training of the new "medical evaluation group". No press release was issued about Dr Lo Cascio's appointment.

- It was the same Dr Lo Cascio who, together with (then) Drs Simon Wessely, Michael Sharpe and Trudie Chalder, spoke at a Symposium on "CFS" entitled "Occupational Health Issues for Employers" held at the London Business School on 17th May 1995, at which attendees were informed that ME/CFS has been called "the malingerer's excuse". Lo Cascio spoke on "Insurance Implications"; Wessely spoke on the "The facts and the myths"; Sharpe spoke on treatment options (exercise and CBT) and Miss Chalder spoke on "Selling the treatment to the patient"

- As reported in Private Eye ("Doctors On Call"; issue 874, 16th June 1995, page 26), UNUM's Chairman, Ward E Graffam, enthused about "*exciting developments*" in Britain: "*The impending changes to the State ill-health benefits system will create unique sales opportunities across the entire disability market and we will be launching a concerted effort to harness the potential in these*"

- As Private Eye noted, with so much less government money going to sick and disabled people, the opportunities for private disability insurers were enormous

- Ten years after being invited to streamline the UK disability benefit system, UNUMProvident sponsored the Labour Party Conference in 2003

- In August 2004 UNUMProvident issued a Press Release reporting a striking 4000% increase in claims for syndromes that are primarily symptom-based, including ME/CFS

- UNUMProvident has been found guilty in numerous high profile legal cases of unwarranted delays in the processing of claims and of wrongful denial of claims, resulting in awards of punitive damages against the company for its improper refusal to pay legitimate claims

- Members of Parliament are on record as being gravely concerned about the difficulties their constituents with ME/CFS face with UNUM, as recorded in the House of Commons debate chaired by Sir Alan Haselhurst on 21st December 1999 (see Hansard 147WH – 166WH). Concerns voiced about various insurance companies included the following:

- *"So extreme are the practices of that company that a UNUM support group has been set up for people in a similar situation. It has 250 members and estimates that 4,000 people are in similar situations throughout the country"*

- *"It is not only people in the United Kingdom who are suffering such problems. There is documented evidence from throughout the United States, where UNUM is the largest company that provides such insurance cover. There is evidence of such cases from Australia and Canada, and I have no doubt that people in other countries also suffer as a result of the sharp practices of UNUM and similar companies"*

- "*All (ME) claimants are sent to a psychiatrist, whose diagnosis is subject to questionable decisions"*

- **"***If they have been treated by an ME specialist who favours another method of diagnosis and treatment, they may find that their disability insurance payments cease"*

- **"***Several patients were forced to attend named psychiatric clinics and to receive cognitive therapy, graded exercise and psychoactive drugs. They were told that if they did not they would lose their pension rights"*

- *"The ombudsman recently turned down Mr. Little's appeal on the ground that ME might not exist as an illness and that, if it did exist, it was of a psychological nature and Mr. Little was therefore in need of psychotherapy"*

The onslaught of UNUMProvident and the Wessely School on people with ME/CFS has been relentless and ever-increasing**.** for example:

2002

In 2002, Dr Peter Dewis, then Chief Medical Officer for UNUMProvident, wrote about the patients whose claims management posed difficulties for UNUMProvident. Dewis joined UNUMProvident in July 2000, having spent 16 years with the UK Department for Social Security, where he held a number of claims assessment, management and policy roles.

In UNUMProvident's 2002 Report "Trends in Health and Disability", Dewis wrote:

"*We frequently emphasise the fact that a medical diagnosis does not equate to a certain level of disability… I have commissioned a number of papers from leaders within the medical profession whose disciplines are particularly relevant to those people…whose claims most frequently pose us difficulties in their management.*

"A paper from Michael Sharpe has reviewed the developments, not only in chronic fatigue syndrome, but also the range of disorders where the symptoms experienced by individual patients appear to be out of proportion with the physical findings or objective evidence of disease.

*"Mansel Aylward who is Chief Medical Advisor to the Department of (*sic*) Work and Pensions has set out the current trends in government strategy relating to both health and social security.*

"I would like to draw out a few specific points…describing those areas which are likely to present us with the greatest challenges.

"My intention would be for this report to be repeated on an annual basis and so become an authoritative and informative document on the current state of medical thinking on those issues which are of greatest importance to us.

"Dr Lipsedge (and) Dr Sharpe have identified the importance of cognitive behaviour therapy of (sic) *influencing the outcome in …chronic fatigue syndrome. This again represents a challenge in ensuring that people are directed towards this approach".*

Not only is the UNUMProvident Report not an authoritative or informative document on ME/CFS, it is factually incorrect.

In the same UNUMProvident 2002 publication, the MRC PACE Trial's Principal Investigator, Michael Sharpe's contribution, entitled "Functional Symptoms and Syndromes: Recent Developments", has become notorious, especially the following quotations:

"It is becoming increasingly clear that the problem of patients who have illness that is not clearly explained by disease is a large one.

"There is a great deal of confusion about what to call such illness. A wide range of general terms has been used including 'hysteria', 'abnormal illness behaviour', 'somatisation' and 'somatoform disorders'. Recently the terms 'medically unexplained symptoms (MUS) and 'functional' symptoms have become popular amongst researchers.

"Classification is also confusing as there are parallel medical and psychiatric classifications. The psychiatric classifications provide alternative diagnoses for the same patients.

"The majority will meet criteria for depressive or anxiety disorders and most of the remainder for somatisation disorders of which hypochondriasis and somatoform disorder have most clinical utility.

"The psychiatric classification has important treatment implications. Because patients may not want a psychiatric diagnosis, this may be missed.

"There is strong evidence that symptoms and disability are shaped by psychological factors. Especially important are the patients' beliefs and fears about their symptoms.

"Possible causal factors in chronic fatigue syndrome:

"PSYCHOLOGICAL: personality, disease attribution, avoidant coping style.

"SOCIAL: information patients receive about the symptoms and how to cope with them; this information may stress the chronicity and promote helplessness. Such unhelpful information is found in 'self-help' books. Unfortunately doctors may be as bad.

"Obstacles to recovery:

"The current system of state benefits, insurance payment and litigation remain potentially major obstacles to effective rehabilitation.

"Furthermore patient groups who champion the interest of individuals with functional complaints (particularly chronic fatigue syndrome) are increasingly influential; they are extremely effective in lobbying politicians. The ME lobby is the best example.

"Functional symptoms are not going to go away. However, the form they take is likely to change. Possible new functional syndromes are likely to include those associated with pollution (chemical, biological and radiological).

"As the authority of medicine to define what is a legitimate illness is diminished, increasingly consumer oriented and privatised doctors will collude with the patient's views that they have a disabling and permanent illness.

"In other words, it may be difficult for those who wish to champion rehabilitation and return to work to 'hold the line' without seeming to be 'anti-patient'.

"It will be imperative that health and social policy address this problem.

*"This will not be easy. However, there are glimmers of progress. An example is recent developments in the politics of CFS. One of the major charities (Action for ME) is aligning itself with an evidence-based approach. These are early days but if this convergence of rehabilitation oriented clinicians and a patient advocacy group is successful, there could be very positive implications for patients and insurers***.**

"Funding of rehabilitation by commercial bodies has begun in the UK (with organisations such as PRISMA) and is likely to continue.

"An increased availability of rehabilitative treatment facilities is highly desirable.

"Both health services and insurers now need to take a more positive approach."

Serving as confirmation of the influence of these psychiatrists, Mansel Aylward's contribution sets out some of the Labour Government "planned initiatives" in the areas of Health and Welfare:

"*From the perspective of the Government's commitment to reform the welfare system…this paper addresses some of the existing and planned initiatives in the areas of Health and Welfare.*

"Under the recently launched NHS Plus initiative the NHS will be encouraged to provide occupational health services in order to improve the health of the workforce and to generate income.

"There is a common interest across several Government Departments in measures which would reduce the high costs of sickness absence and improve the quality and availability of …rehabilitation.

"The Government shares an interest…in the public, private and voluntary sectors which have a stake in the development of more effective models of rehabilitation.

"Growth in benefit recipients due to mental and behavioural disorders has been rapid during the last five years….These analyses point to growth in mental and behavioural disorders…. Another interpretation might be a migration in the diagnostic label from other medical conditions to 'mental health problems'.

"The Government's twin objectives of raising productivity and achieving full employment aim to increase the wealth-creating potential of the economy…Reduction in public spending on benefit payments is a distinct advantage arising out of the full employment objective".

2003

Peter Hallligan (Professor of Neuropsychology, Cardiff University) and Mansel Aylward (then still Chief Medical Advisor at the DWP) jointly organised a meeting on 12th May 2003 (perhaps coincidentally, as 12th May is national ME Awareness Day) entitled "The power of belief: psychosocial impact on illness, disability and Medicine".

It was reported by Tom Hughes, Consultant Neurologist at the University Hospital of Wales, in the following terms:

"*I attended this conference in the hope of acquiring some new perspective on those patients with significant disability in whom – from a neurological perspective – we are unable to find a cause….I felt the need to acquire some new behavioural software to help me deal with these patients.*

"Professor Peter Salmon (University of Liverpool) talked about the patients' beliefs regarding their medically unexplained symptoms and the implications for diagnosis and treatment. Whilst some sympathy was expressed for the general practitioner….the conclusion seemed to be that symptomatic interventions are inappropriate.

"Professor Derek Wade (University of Oxford) gave a lecture entitled 'Enablement: Remarketing Socio-medical expectations in Rehabilitation'. ***Enablement is the new alternative word to rehabilitation and I think it's really going to take off.***

"Professor Kim Burton (Huddersfield) emphasised the importance of psychosocial factors in maintaining persistent symptoms and disability and how these can be identified. ***The role of inappropriate or erroneous beliefs held by patient and practitioner are important obstacles to recovery".***

2005

The Report of Dr Michael O'Donnell, Chief Medical Officer of UNUMProvident ("Evolving: the way we look at claims"), states:

"In everyday life, all of us experience symptoms of one sort or another….What determines how a person reacts to a symptom…?

"In the past it has been considered that medicine alone could supply the answer about how to measure incapacity….There are many… examples of how the medical model of disability fails to fully explain incapacity.

"The Biopsychosocial (BPS) model attempts to take a holistic view of incapacity and disability…We know that…factors such as…beliefs about causation…are more important predictors of long-term absence…

"We are now finding that as we better understand the BPS model (our current claims team structure) may be impeding our ability to manage claims in the best possible way….With effect from 07.11.2005…we shall have psychiatric expertise much more readily available to all CMCs (Claims Management Specialists). This will enable us to identify much more readily those cases where …psychiatric illness lies behind or complicates the medical presentation of incapacity.

"At UNUMProvident, we believe that we have always been at the leading edge of disability assessment and management.

"We know that our views and understanding are not yet in the mainstream of doctors' thinking, but Government Policy is moving in the same direction.

"It will not be many years before the rest of medicine follows our lead".

2006

In the next UNUMProvident report in the same series ("Enabling: a holistic view of health") Michael O'Donnell reiterated the same message and emphasised how much UNUMProvident had learnt from academic colleagues at the UNUMProvident Centre for Psychosocial and Disability Research at Cardiff (ie. from Mansel Aylward):

"*In a previous publication (Evolving, November 2005) we told you about changes (that) reflect the knowledge we have gained at UNUMProvident about the complex interactions between ill health and behaviour.*

"We believe that the biopsychosocial model of disability provides a complete view of illness, sickness and disease.

"It is important to understand why we believe the biopsychosocial model of disability is so important…the older medical model provides a very incomplete view of what lies behind sickness and incapacity…There is more to disability and incapacity than just illness or a disease. We know, for example (that) beliefs about causation….are more important predictors of long-term absence….

"Many people confuse illness with disease, when in fact they are distinct.

"By definition, some illnesses occur in the absence of disease. Irritable Bowel Syndrome is one such illness.

"What determines the subjective experience? Previous life experience will be important. Were they brought up by over-protective parents and developed negative and fearful expectations of life?

"(Our) application form…contains a series of behaviour-based questions….We believe our move away from diagnosis-based underwriting to a decision-making process linked far more closely to applicant behaviour and attitude is a significant first step….An applicant's GP consultation pattern, when added to a history of medically unexplained symptoms, may well steer the underwriter to an adverse terms decision.

"The biopsychosocial model tells us that what keeps people off sick often has little or no relation to what they went off with in the first place. Early intervention can prevent harmful ideas or beliefs becoming embedded.

"At UNUMProvident we believe that the only way to ensure that our claimants and customers receive the help they really need is by understanding what lies behind illness and incapacity.

" Just understanding is not enough, we have to ensure that this understanding is correctly applied to ensure that we all reap the benefit".

2007

The next publication in the series ("Enhancing our claims management service") delivered the same sermon:

"*In 2005 we introduced the concept of the biopsychosocial model….We explained that through our links with the UNUM Centre for Psychosocial and Disability Research at Cardiff University, we had grown to wholeheartedly embrace the BPS model.*

"We are continuing to build on what has proven to be a very successful model.

"UNUM has been specialising in Income Protection since 1970. As our knowledge, experience and understanding of this complex area has grown, so too has our hunger to drive and enhance the market in terms of delivering leading edge theories (and) concepts".

2007

In November 2007 Mansel Aylward wrote the Monthly Editorial for HCB Group News. HCB stands for Health Claims Bureau Group and incorporates James Harris Investigations. Aylward is a non-executive Director of HCB. Another non-executive Director is Peter Le Beau, who previously worked at the re-insurer Swiss Re (where Peter White is Chief Medical Officer) and when at Swiss Re was one of the first people to use the services of HCB.

Aylward's Editorial is entitled "Changing the culture about work, health, and inactivity: challenging the path to economic activity" and he says:

"*The social contexts of economic inactivity…must be fully recognised and soundly addressed if the desirable shift in culture about work and health is to be attained.*

"A person's past social experiences…are written into the body's physiology and pathology.

"Tackling effectively the social determinants of…health is not a matter for public and occupational health alone. In the United Kingdom it is central to the Government's realisation of its aspiration for an 80% employment rate for the working age population.

*"**The great majority of these health problems are largely subjective complaints with limited evidence of disease and frequently associated with psychosocial influences.***

"Psychological and social factors aggravate and perpetuate ill health and disability, and act as barriers to recovery and return to work.

"Persuaded by the formidable evidence in support of a bio-psycho-social approach for return to work interventions, the British Government began a series of pilot studies in 2004. This Pathways to Work (PTW) initiative prominently featured cognitive and educational methods, modification of illness-behaviours, fear-avoidance beliefs and had a clear work focus.

"The results of this initiative have been most encouraging to the extent that the British Government has recently extended PTW throughout Great Britain.

"The need to modify beliefs and behaviours in the achievement of the PTW initiative went well beyond the target population of benefit recipients by engaging successfully with senior politicians and civil servants, health care professionals, employers and other stakeholders.

"Methods for securing engagement with …the stakeholders were highly dependent on a structured, robust and authoritative communications strategy (and) providing compelling evidence-based arguments that barriers to return to work resided not only in dealing with health problems alone but tackling psychological social and cultural constraints impacting upon an individual's beliefs and behaviours".

When the Green Paper "A New Deal for Welfare: empowering people to work" was released in January 2006, it was analysed and assessed by Alison Ravetz, Professor Emeritus of Leeds Metropolitan University who writes on welfare reform, who in March 2006 wrote "An independent assessment of the arguments for proposed Incapacity Benefit reform", from which the following quotations are taken:

"In the lead-up to the Green Paper and its publication on 24th January 2006, the media had a field-day at the expense of those enduring illness and disability, conveying the impression that they were scroungers living at public expense. The mismatch between this and my personal experience of severe, long-term illness within my own family led me to look into the reportedly successful 'Pathways to Work'. Seeing the weakness of the evidence for their success, I was curious to look into the body of research and theory on which the Green Paper is based, which is used to validate its proposals".

Ravetz soon found that the source of much of the Green Paper was "The Scientific and Conceptual Basis of Incapacity Benefits" (TSO, 2005) written by Waddell and Aylward and published by the DWP, who were asserting that the then system of benefits was *"based on the wrong model of sickness / disability – the 'medical model' ".*

"The aim was nothing less than a reversal of the common attitude towards sickness, disability, and the capacity for work.

"In practical terms, it meant opting out by the State of responsibility for a large section – estimated at two-thirds – of those afflicted by illness or disability.

"Its proposals appear to be backed by voluminous reports from the DWP, DoH, OECD and (the) Prime Minister's Policy Unit. Most of these publications bear the hallmarks of academic authority and objectivity. They are presented

with what look like exhaustive bibliographies, reference, footnotes, tables, graphs, diagrams and statistics, leading readers to suppose that arguments for reform are supported by inexorable logic, and swaying them towards the conclusions reached by tedious repetitions and platitudes.

"On closer examination, it appears that this entire body of work is largely self-referential.

"It appeals for validation to itself and all is framed within the same policy agenda.

"The Scientific and Conceptual Basis of Incapacity Benefits (authors Gordon Waddell and Mansel Aylward) is particularly interesting in this connection (and) it is useful for revealing the thinking behind the Green Paper. Its source is the UNUMProvident Centre for Psychosocial and Disability Research located in Cardiff University since 2004. (Aylward's) remit is 'to develop specific lines of research into the psychosocial factors related to disability, vocational rehabilitation, and the ill-health behaviours which impact on work and employment'.

"UNUMProvident is the largest disability insurance company in the world and is involved in a number of lawsuits for 'bad faith' in refusing to honour disability insurance claims.

*"**This reinforces the caution against taking this apparently impressive body of work at face value. It is not research undertaken in the spirit of open enquiry. It is commissioned research and, as such, pre-disposed towards ideologically determined outcomes**.*

"GPs, who first certify claimants, do not 'understand the importance of work for health'. This reviews different ways of bypassing them, including access to confidential GP records…. 'For common health problems, the doctors' opinion…is unfounded, of limited value and can be counter-productive' (The Scientific and Conceptual Basis of Incapacity Benefits, p 145-146)".

Commenting on the political philosophy underpinning this "reform", Ravetz says:

"The broad context is the Government's 'new vision' of a reformed welfare state, where relations between state and citizen constitute a 'contract' in which rights of the citizen are balanced by obligations (and) the sick and disabled are not exempt from this contract.

"Under the 'contract', the obligations of claimants are to 'recognise that symptoms, feeling unwell, sickness and incapacity are not the same'. To this is added: 'The greater the subjectivity and personal / psychological elements in incapacity, the greater the degree of personal responsibility'. Should they fail to carry out their obligations, claimants must be subject to sanctions.

"The assumptions about illness/disability made (by Waddell and Aylward) and in the Green Paper must give rise to concerns. The whole emphasis is on de-coupling health problems and medical conditions from unfitness for work.

"We are expected to be impressed by the unacceptable and spiralling numbers of claimants…but we are not presented (as would be the case in genuinely objective research) with the data from which to evaluate the conclusions drawn.

"Claimants are depicted as a drag on the economy and money spent on them as good as poured into a black hole.

"The underlying philosophy belittles sick and disabled people. By implying that they are parasites, it excludes them more insidiously from the body politic than the system it seeks to replace.

"(The) Case Management Programmes (CMPs) are based mainly on cognitive behavioural therapy.

"Another crux is relying on CMPs as a tool for coaxing people out of patterns of 'illness behaviour'. They are applied by occupational and physio- therapists, who lack expert knowledge of the diseases clients may have. They make much use of watered-down cognitive behavioural therapy which, delivered inexpertly and in group situations, can add to the

anxiety and guilt of people with serious conditions by suggesting that they are causing their own illnesses, when all along they are suffering from insufficiently understood but real diseases.

"The personal adviser will have a worrying degree of power over the lives of people who are by definition vulnerable. ***GPs will no longer be looked to for independent, expert assessments****.*

"Sadly, serious disease and disability cannot be glossed out of existence by platitudes like 'work is the best therapy'.

"People will not find comfort in the Government's refusal to acknowledge the medical reality of their conditions, or their own huge efforts to cope with these.

*"****In effect, though claiming to address the future, the DWP is turning the clock back to a time before National Insurance, when the cost of sickness was borne by the individual and the family. The cost to those people and their families will be incalculable****".*

Professor Ravetz followed up her 2006 document with an article in The New Statesman published on 1st May 2008 entitled "Is Labour abolishing illness?" (http://www.newstatesman.com/politics/2008/05/work-benefit-claimants-reform):

"We are told that we are footing an outrageously escalating bill for 2.4 million people, a million of whom shouldn't be on the benefit at all. The true picture is somewhat different. The unreported version is that only 1.4 million of the 2.4 million actually receive any payment (and) the audited estimate of fraud is under 1 per cent – the lowest of any part of the social security system.

"A main selling point of the reform was the great savings it would bring. Delivery is being farmed out to private agencies paid by results – which means, of course, the setting of targets. The next few years will be a bad time to succumb to a serious disease, particularly a neurological one that does not have obvious outward symptoms.

"People must be healthier, which proves that huge numbers are exploiting a slack and obsolete system. Who is to blame? It can only be the self-indulgent, who fancy themselves sicker than they really are, and complacent GPs who let them think they are too ill to work.

"The Government's declared mission is …to overturn a culture based on the 'medical model' of illness.

"Doctors — so often the refuge of desperate people trying to find out what is wrong with them – should as far as possible be excluded from the process.

"Deliberate rejection of the 'medical model' deprives us of all we might have learned (from the wealth of data available) of the impact of illness on our society.

"I have scratched my head long and hard over this reform…because so much of its theory and rhetoric contradicts my own experience of chronically and seriously ill family members…and years of involvement in action groups for chronic fatigue conditions. All this has impressed me with the courage of many who live with horrible complaints, the sheer hard work involved in their day-to-day coping, their relentless search for any amelioration, let alone cure.

"I have witnessed, too, and at close quarters, the hurt and stress of living difficult lives in a perpetual culture of disbelief and threat, where some of the most valiant are blamed for their conditions and conflated with the alleged 'can't work, won't work' unemployed.

"For the message of the reform that comes across is that a person is valued only as a productive unit….those too ill to work are outside society, and money spent on them is wasted. Sickness, disablement and inability to work have no place in a modern society – they can't and shouldn't be afforded".

To date, MPs' postbags continue to bulge with horror stories from their constituents about the same issue:

- *"Swiss Life forced her to see a psychiatrist with known views on the causation of ME by threatening to stop her payments; but she has been refused sight of the psychiatrist's report"*

- *"I am alarmed to hear from hon. Members that insurance companies can insist on a treatment set out by their medical assessors, who are doctors employed by them"*

- **"***I was interested to learn that UNUM has advised the Benefits Agency's medical division. That explains some of the unimpressive decisions made by doctors on behalf of the Benefits Agency".*

Mindful of the fact that the Wessely School (and hence the NICE Guideline on "CFS/ME") specifically recommend that no tests should be carried out to confirm the diagnosis, it should be recalled that if the correct investigations were permitted to be carried out in the UK (immune, HPA axis and mitochondrial function; enteroviral serology; SPECT scans etc) then the psychiatrists' paymasters could not legitimately disregard such evidence and company profits would plummet.

The insurance industry is determined that this must not happen: UNUM's "Chronic Fatigue Syndrome Management Plan" (dated 4th April 1995 and authored by Dr Carolyn L Jackson) makes this clear: *"UNUM stands to lose millions if we do not move quickly to address this increasing problem".* Fourteen years later, that is exactly what UNUMProvident and other insurers served by the Wessely School are doing most effectively.

The MRC PACE Trial Manuals appears to show just how this plan is being put into action.

Appendix V: Professor Mansel Aylward

In December 2003 Professor Mansel Aylward gave evidence to the Public Accounts Committee's enquiry into progress in improving the medical assessment of incapacity and disability benefits. The Committee was very concerned that 51% of appeals against Incapacity Benefit and DLA (Disability Living Allowance) decisions were being won by claimants. There was clear scepticism by the Committee about the skills of the privatised doctors contracted to work for the DWP. According to the evidence given at this hearing, these doctors receive between £50 - £70 per medical, which would allow them to earn in excess of £100,000 per year.

Professor Aylward leapt to the defence of the private doctors used by the DWP: his evidence was that in his professional opinion, the privatised (DWP) doctors who refused claims had got it right and the appeal tribunals had got it wrong, as the privatised (DWP) doctors were better trained.

When asked why this alleged problem of poor training of appeal tribunal doctors apparently persisted, Aylward responded: *"I am working very closely with the President of the Appeals Service to ensure that the difference is remedied*".

By this, Aylward was saying that in his opinion there was a problem with the training and validation of Appeals Service doctors, and also that it was accepted that this was the case because Judge Harris, President of the Appeals Service doctors, was working with him to remedy the problem.

Alan Williams MP then asked Aylward if he had fed his concerns on this issue into the system, and at what level had he fed his concerns into the system. Aylward replied: *"I fed it in at the highest level. I fed it in at the highest level in the Appeals Service. I have made my colleagues in DWP aware of it".*

At Benefits and Work (www.benefitsandwork.co.uk), Steve Donnison was very concerned at the possibility that someone (ie. Aylward) appeared to be in a position to influence the President of the Appeals Service and possibly persuade him that the Appeals Service doctors, like DWP doctors, should be trained by a privatised company in order to reduce the number of claimants winning appeals.

Donnison therefore sought clarification from Aylward and under the Freedom of Information Act asked to see copies of any communications between him and Judge Harris about Aylward's stated concerns over the poor quality of the Appeals Service doctors.

Aylward's reply was curious: *"I have not personally written to Judge Harris or anyone else within or connected to the Appeals Service".*

Mindful of Aylward's evidence to the Public Accounts Committee, Donnison again asked Aylward for information about the work he had undertaken with Judge Harris and any documents relating to it. Given Aylward's evidence to the Committee that he was working very closely with Judge Harris and that he had fed his concerns into the system at the highest level, Aylward's written reply was astonishing: *"I have no documents or communications. The limited feedback I have given to the Appeals Service has been given verbally*".

The disparity in Aylward's evidence is not an insignificant matter because the apparent intention of his evidence to the Committee appeared to be the undermining of MPs' faith in the judgments of the Appeals Service doctors (who allegedly allowed undeserving claimants, including those with ME/CFS, to receive State benefits).

Whether or not the Chief Medical Advisor at the DWP misled a House of Commons Select Committee is a grave matter.

APPENDIX VI: The Wessely' School's autopoietic theory of their "CBT model".

In 2007, two of the PACE Trial Principal Investigators, Professors Trudie Chalder and Michael Sharpe, together with mental nurse Vincent Deary (described in the PACE Trial literature as a "*First wave therapist (CBT)"* and as a contributor to the treatment design), published a paper entitled "The cognitive behavioural model of medically unexplained symptoms: A theoretical and empirical review" (Clinical Psychology Review 2007:27:7:781-797) in which they explain the rationale for their "CBT model" of CFS.

These authors conducted a literature search of Medline and Psychinfo from 1966 to 2007 using MUS (medically unexplained symptoms) *"and related terms"*. They reviewed *"all relevant articles"* and their search was then limited in stages by CBT, condition, treatment and type of trial. They say they found evidence for *"genetic, neurological, psychophysiological, immunological, personality, attentional, attributional, affective, behavioural, social and inter-personal factors in the onset and maintenance of MUS"*.

From this, they deduce that MUS are the result of "*individual factors and their autopoietic interaction (as hypothesised by the CBT model"* (surely *"individual factors"* is broad enough to mean that virtually anything can cause MUS?).

However, these authors mostly disregard the genetic, neurological and immunological factors and concentrate on the psychosocial factors as constituents of their "CBT model".

The authors say: *"The evidence for the contribution of individual factors, and their autopoietic interaction in MUS (as hypothesised by the cognitive behavioural model) is examined. The evidence from the treatment trial of CBT for MUS, CFS and IBS is reviewed from an experimental test of the cognitive behavioural models"*.

The "CBT model" cannot, however, be tested experimentally; all that can be said is that CBT may be a useful intervention in some subjects in some disorders, **but this does not provide evidence for a "CBT model" of CFS or IBS.**

However, the authors state: "*We conclude that a broadly conceptualised cognitive behavioural model of MUS suggests a novel and plausible mechanism of symptoms generation and has heuristic value"*.

Deary has previously written about heuristic value. What he seems to be saying is that if one approaches the treatment of a patient heuristically – literally, by trial and error – one may find practical ways to help the patient.

Such an approach ignores causality – for example, giving a patient laudanum tincture will make them feel better by lessening their pain **but it does not tell one anything about the cause of their pain.** If, whenever one reads the "CBT model" one replaces it with the "laudanum tincture model" one will get the same result, indicating that CBT does not take the cause of the disease into account.

The authors then state: " *'The term medically unexplained symptoms names a predicament, not a specific disorder' wrote Kirmayer, Groleau, Looper and Dao (2004)"*. Although Deary, Chalder and Sharpe rely on it, this is logically wrong. Medically unexplained symptoms in an individual may in fact refer to a specific disorder – until an explanation is found, it is unknown what type of disorder is being described. It is also the case that since MUS contains whatever remains from medically explained investigation, it is most unlikely to be one disorder. Furthermore, it is incorrect to describe MUS as a "*predicament"*. For example, before the pathoaetiology of Parkinson's Disease (PD) was established, using the authors' model PD would have been considered a MUS, and therefore, by their reasoning, a "*predicament"*. Would they refer to PD as a *"predicament"* today? This assumes that any symptom that has not yet been explained by contemporary biomedical knowledge will always be "medically unexplained", which is clearly untrue (but the Wessely School are strongly opposed to seeking biomedical evidence for what they insist are "medically unexplained" -- and therefore psychosomatic -- symptoms: see above).

Deary et al continue: "*In the papers we have reviewed it is used in three overlapping ways: (a) to refer to the occurrence of symptoms in the absence of obvious pathology* (there may be no obvious pathology, but they do not consider the possibility of occult pathology); *(b) to refer to individual clinical syndromes such as CFS and IBS* (this is inconsistent -- having said that MUS *"names a predicament, not a specific disorder"*, in their point (b) Deary et al describe CFS and IBS as specific disorders, ie. as "*individual clinical syndromes"*); *(c) to refer to a subset of the DSM-IV somatoform disorders category*" (but DSM-IV does not include CFS as a somatoform disorder).

Deary et al claim that: *"there is consensus that a cognitive behavioural therapy (CBT) approach offers a useful explanatory model of MUS…and an effective treatment".* Such a statement has no validity because *"an approach"* does not and cannot offer *"a useful explanatory model"*.

Furthermore, there is no consensus that it provides *"a useful explanatory model"*; equally there is no consensus that CBT is *"an effective treatment"*. Deary et al then claim that: "*These recent reviews have validated the efficacy of CBT* (the efficacy of CBT for ME/CFS patients has not been validated) *but there has been less focus on the model on which these treatments are based"* (perhaps because CBT is a therapy, not a model).

Although Deary et al refer to their "CBT model" of MUS (which does not exist) and whilst there may be empirical evidence that CBT can help some people with a behavioural diagnosis, this tells us nothing about the underlying cause of ME/CFS or indeed of any other illnesses in which CBT may be employed as an adjunctive therapy, be it cancer, multiple sclerosis or diabetes.

The authors continue: "*We will then summarise the evidence for its effectiveness as a treatment with a view to how this evidence can contribute to our evaluation of the CBT models"*, which seems to indicate that Deary, Chalder and Sharpe do not accept that evidence of efficacy of CBT in some patients (who are likely to suffer not from ME/CFS but from chronic "fatigue") proves nothing about their "CBT model" of causation in ME/CFS or IBS.

More internal contradictions follow: the authors state: "*For the purposes of our literature search we adopted a broad definition of MUS…we looked specifically at IBS and CFS. Pain was largely excluded because the scope of the literature would have made the review unwieldy"*. Clearly therefore, the authors did not conduct a literature search that adopted *"a broad definition of MUS"*. They focused on IBS and CFS and they deliberately excluded anything they considered "*unwieldy"*. Their study thus can have no academic value because their terms of reference are elastic and arbitrary.

Deary et al say that they employed the search terms *"functional symptoms; functional syndromes; functional illness; functional somatic symptoms; functional somatic syndromes; functional somatic illness and medically unexplained illness"* which means that the authors intentionally skewed their results towards psychosomatic disorders, whereas neither ME/CFS nor IBS is a psychosomatic disorder.

Deary et al say: "*As a first analytic step, we reviewed all the abstracts and reports obtained by using 'Medically (near) Unexplained (near) Symptoms' as a search term"*. They then claim that this material was *"used to conduct the narrative review of the CBT model of MUS"*, which is an unsustainable claim because it is not possible to test *"the CBT model"* of causation of MUS, only the efficacy or otherwise of CBT in loosely defined patients (who may or may not have ME).

Deary et al then claim that their "*body of evidence"* contributed to their *"understanding of the model"* (no body of evidence can contribute to the understanding of a model that does not exist); all it proves is that Deary, Chalder and Sharpe were reading the literature with a predefined agenda – ie. they were looking for evidence to support their own ideological convictions about ME/CFS and IBS.

In order to validate their own beliefs, Deary et al have fallen back on the theory of autopoiesis as the explanation for their putative model.

They explain that historically, the classical *"CBT model"* of emotional distress as proposed by Beck distinguished between predispositions and precipitants, and perpetuating cognitive, behavioural, affective and physiological factors, and that the "*CBT model retains this general structure and its 'three Ps': predisposing, precipitating and perpetuating factors"*.

Deary et al say: *"Treatment tends to initially focus on the perpetuating cycle, attempting to dismantle the self-maintaining interlock of cognitive, behavioural and physiological responses hypothesised to perpetuate the symptoms"*.

According to Deary et al, the "*sine qua non of any CBT model is a vicious circle, the hypothesis that a self-perpetuating interaction between different domains maintains symptoms*" and they postulate that *"the CBT models of MUS, IBS and CFS propose a model of perpetuation that is autopoietic"*. Quoting Valera (2005), Deary et al define autopoiesis as: "*the process whereby an organization produces itself…an autonomous and self-maintaining unity"*. If Deary et al were meaning to refer to the "Father" of autopoiesis, and the person who introduced the concept of autopoiesis to biology, then that person is Francisco Varela (not Valera), and Varela died in 2001, so it is not clear why Deary et al cite a website and not a peer-reviewed paper for their autopoiesis reference. Furthermore, their citation for "*Valera (2005*)" does not appear on the website in question (http://pespmc1.vub.ac.be/ASC/AUTOPOIESIS.html).

Deary et al then say that *"The CBT model of perpetuation differs from a more generic biopsychosocial model by proposing a unique autopoietic interaction of cognitive, behavioural and physiological factors for each individual….symptoms are (assumed to be) generated not by one disease process but by the interaction of (cognitive, behavioural and physiological) factors"*. Deary et al say they considered as examples of the "CBT model" of MUS *"all models which propose such a process"* (notably, not a few of the considered papers were Wessely School self-references).

The authors say that although there are varying degrees of evidence for each of the components of their model, *"what is lacking is solid proof of their interaction in vicious circles, although all of the models reviewed* (including their own) ***assume*** *this interaction"*.

Despite their own "assumption", claiming "*coherence"* of their "CBT model", Deary et al say: *"the key feature of CBT model is that these individual components become locked into an autopoietic cycle"* and they hypothesise that in "*vulnerable individuals,* ***such as those who are over-active****, CFS is precipitated by life events or viruses leading to an autopoietic cycle in which physiological changes, illness beliefs,* ***reduced activity****, sleep disturbance, distress, medical uncertainty and lack of guidance interact to maintain symptoms. The evidence supports some of the individual dots in this picture but not yet the lines between them"*.

Their construct of causation clearly includes factors that are mutually exclusive (overactivity as well as underactivity), which begs the question that their model is all-embracing and was designed to ensure it can never be disproven.

Deary et al then state that: *"what makes the CBT model so difficult to test may also be one of its chief strengths: it is in many ways a meta-model to join the dots of whatever factors each patient presents. Indeed, factors that are neither strictly cognitive nor behavioural but have been found to be important (for instance, social support* [citing Chalder 1998] *or benefit receipt can be incorporated into this structure as perpetuating factors"*.

Two points arise:

(i) the authors do not consider that many people whose lives are wrecked by ME/CFS <u>are not claiming either state benefits or permanent health insurance</u>, so how do <u>they</u> fit into their "CBT model", given that two of the allegedly perpetuating factors do not apply to them?

(ii) the authors concede that they cannot join the dots to produce the full picture, yet they still hang their beliefs about their model on individual dots, claiming that some of the dots -- especially social support and

benefit receipt -- are important. Even though they admit that their model cannot be tested, they have stated that the dismantling of social support, including benefits on which sick people rely, may be necessary for "recovery". How does the removal of vital support assist recovery in any disorder?

Deary et al continue: "*the evidence does support the conclusion that MUS in general, and IBS and CFS specifically, are multi-factorial conditions* ***caused and perpetuated*** *by several distinct processes…the research bears out the over-arching CBT hypothesis that the autopoietic interaction of distinct but linked systems could serve to produce physical symptoms in the absence of physical pathology",* a statement that seems to reveal the extent of the authors' lack of biomedical knowledge about ME/CFS.

Deary et al state: "*In CFS inconsistent and reduced activity, disturbed sleep and catastrophic beliefs regarding activity and symptoms are the most commonly identified set of factors and therapeutic targets"* (commonly identified and targeted by whom? Certainly not by biomedical scientists and clinicians).

In the section that is specifically on chronic fatigue syndrome, the authors state: "*It is hard to disentangle the active ingredients in these treatments* (CBT and GET). *The CBT tends to involve pacing, graded increases in activity, sometimes exercise, work on a variety of cognitions including perfectionist beliefs, catastrophic illness beliefs and schema work. The GET trials provide a relatively more focused intervention, and we could easily conclude that the reversal of deconditioning is the effective component of this form of treatment".*

Given the previous well-documented hostility of the Wessely School towards rest and pacing, not only in the literature but also in the press and in the magazines of the patients' charities, the authors' claim about pacing in their 2007 paper is noteworthy, as it seems to be only since they were awarded millions of pounds sterling for their PACE Trial that they have revised their attitude towards it and have recorded their changed attitude in an article published during the life of the PACE Trial.

Deary et al say: "*We suggest that we are now at the stage where research should pay more attention to some of the components of the model and their interaction…The CBT model of MUS offers a previously undescribed illness mechanism maintaining a distinct group of disorders that we might call autopoietic conditions. Treatment is aimed at…dismantling the autopoietic mechanism by making changes in target areas".*

Having noted that Hotopf (a colleague and frequent co-author with Wessely) has compared the role of doctors in MUS to the role of parents of sick children, and having stated that *"illness related beliefs have also emerged as potentially important factors in the maintenance of symptoms",* Deary et al end their paper thus: "*Hotopf (2004) has drawn our attention to the vital role that both doctors and parents* (most people with ME/CFS are middle-aged and their parents are deceased) *can play in the development, or prevention, of MUS…The right advice derived from a collaboratively constructed model of symptoms experience could be crucial in preventing or ameliorating MUS. In the CBT model, we may just have the means to do this".*

Deary et al make no mention that in 1996 Scheper and Scheper argued convincingly that the autopoietic system theory as developed by Maturana and Varela is unscientific (Behavioural Science: January 1996:41:1) and that the autopoietic theory is ignored in contemporary biology because the theory's core constructs cannot be determined, which means that it cannot be empirically tested. Scheper and Scheper concluded that the autopoietic theory has no explanatory power (ie. theoretical models that cannot be empirically tested do not have explanatory power, because any theoretical model that claims to provide explanations of empirical phenomena must be testable).

Scheper and Scheper are clear; having noted that the Maturana and Varela autopoietic concept *"receives much attention across the behavioural sciences"* but having carried out an autopsy on autopoiesis, they conclude about those who adhere to the notion of autopioesis: "*we believe that they should rethink their use of it. The version of autopoiesis as proposed by Maturana and Varela is unscientific, which means that it cannot be used as a suitable reference in scientific endeavours".*

Why would two PACE Trial Principal Investigators and a "First wave" CBT therapist who was involved both with the design of the PACE Trial and with the Manuals have resorted to a theory that was shown to have been discredited eleven years before their own paper was published?

A further question might be to ask if there were any Wessely School members acting as referees for that issue of Clinical Psychology Review?

In slide 71 of his powerpoint presentation "Why David Healy is wrong" (Searching for Gold Standards: http://www.lse.ac.uk/collections/BIOS/pdf/rcts/Wessely.pdf), Simon Wessely himself noted that in 1996 (the same year that the autopoiesis theory was discredited), Clare Francis, a round-the-world yachtswoman who developed ME and who is President of the charity Action for ME, went on record thus:

"***Psychiatry is opinion dressed up as science***".

If papers such as this one by key people in the PACE Trial are the essence of psychiatry, it is not difficult to agree.

APPENDIX VII: Tactics of denial used by the Wessely School

Denial of the known and available evidence in general

Denial of existing evidence is currently popular by those who see themselves as "revisionists", and such people are extremely dangerous, as they seem to believe that they and their like-minded colleagues alone have the prerogative to define reality.

On 29th April 2000 Channel Four transmitted a programme entitled "Denying the Holocaust" which revealed the tactics used by "deniers" of the truth (in that case, the reality of the Holocaust).

Whilst in no way comparing the suffering and atrocities imposed upon Holocaust victims with the suffering imposed upon those with ME/CFS by doctors who do not believe in it, it may nevertheless be salutary to examine the similarities in the tactics and methods used by "deniers" and "revisionists" of whatever discipline.

Referring to David Irving (the subject of the lengthy legal action involving Penguin Books and Professor Deborah Lipstadt, who was also the subject of the programme). Lipstadt branded Irving *"one of the most dangerous of the men who call themselves revisionists".* The narrator said *"familiar with (the)…evidence, he bends it until it conforms to his ideological leanings and political agenda".*

Such allegations have been made about Wessely in relation to what he publishes about ME/CFS.

Tactics used by "deniers" were identified in the programme as including the following:

manipulation, distortion, deliberately portraying things differently from what is known, falsifying facts, invention, misquotation, suppression, illegitimate interpretation, political re-modelling, exploiting public ignorance and intimidation.

Deniers take liberties with facts, and what is omitted is often more significant than what is included.

A falsifier uses many different means but all these techniques have the same effect ---falsification of the truth and denial of reality.

Other tactics include the following :

- deniers aggressively challenge others' views, claiming that others have no proof, and challenge them to validate the established facts and to produce proof to standards specified by the deniers themselves but to which they do not require their *own* "evidence" to subscribe
- deniers claim that "pressure groups" are active against them and are attacking both them and the truth
- deniers claim that there are "orchestrated campaigns" against them
- deniers agree, prepare and organise as a matter of policy a systematic strategy amongst themselves
- deniers show a readiness to jump to conclusions on every occasion
- deniers endeavour to rationalise their own ideology and for their own ideological reasons they persistently and deliberately misrepresent and manipulate the established evidence
- deniers fly in the face of the available evidence

- deniers engage in "complete deniability" which has nothing to do with genuine scholarly research.

Tactics of denial used in relation to ME/CFS as a physical disorder

Revisionism and denying known evidence in medicine is nowhere more apparent than in the case of ME/CFS, and the choice of Government medical advisers is a matter of great economic impact.

To policy makers and physicians in a cash-strapped NHS, the advantages of denial must seem attractive. The last thing needed is a disease which threatens the health of hundreds of thousands if not millions world-wide, so accepting advice which promotes the view that the condition in question is neither new nor particularly disabling (and that the disorder is largely self-perpetuated) makes instant economic sense, especially if the advice also recommends that granting state benefits to those affected would be not only inappropriate but counter-productive.

In ME/CFS, denial is directed at undermining the experience and expertise of doctors who hold different views from Wessely School psychiatrists, for example, Wessely comprehensively dismissed the views of Professor Paul Cheney (see Section 2 above) and stated that all the neurologists Wessely knows agree with him (ie. that he is right about the nature of "CFS/ME" and others who hold different views are wrong). This may make it less likely that any informed neurologist who does not agree with Wessely will speak out against his views for fear of being ostracised and made to look foolish.

In medicine, denial ought to be very rare due to the peer-review system, but in the case of ME/CFS, many peer-reviewers and editors of journals appear to share the same views as the deniers, so that articles and research papers which show a lack of objectivity and which misrepresent the existing literature and which make unsubstantiated claims abound, with the consequence that readers are misled.

In the UK ME/CFS literature (mostly as a result of the assiduous activities of psychiatrists of the Wessely School), there is evidence of a systematic attempt to deny the severity of the symptoms, the role of external causes and the nature of the illness. Such is the profusion of articles, reports and research papers produced by this group of psychiatrists that there is now a widespread belief that ME/CFS is not a disorder which requires money to be spent on specialist tests or on expensive virological or immunological research, let alone on long-term sickness benefits.

It may be informative to compare the tactics of denial listed above as identified in the TV programme with a selection of methods and tactics used by those engaged in denial activity relating to ME:

- Deniers consistently ignore existing evidence which contradicts their own preferred theories: they disregard evidence, they misconstrue findings, they distort figures and they speculate

- Deniers apply a double standard to the evidence --- they support their own claims with a select choice of studies, with flawed research (ie. with research which has been *shown* to be flawed in the medical literature), and with a mass of generalisations, whilst insisting that the opposition provides irrefutable proof. These authors down-play and attempt to overlook inconsistencies in their own research

- Deniers challenge the expertise of those with whom they disagree, implying that their own claims are based on balanced scientific scholarship whilst those of others are based only on myth

- Deniers portray sufferers as *victimisers*, claiming that it is *patients* who are guilty of targeting *psychiatrists*; who then portray themselves as the vulnerable and wronged group. There is reference to "vicious campaigns" organised by "pressure groups" and to unreasoned hostility on the part of the patients

- Deniers minimise or trivialise the distress and suffering of those with ME/CFS, alleging that patients exaggerate their symptoms and suffering

- Deniers promote the view that patients have only themselves to blame, and that the problem is therefore not external but internal

- Deniers often include a totally reasonable and uncontroversial supposition, (for instance, that decisions must be based upon the best evidence), which gives the impression that their other arguments must be equally reasonable and valid

- Deniers often suggest or imply that patients are motivated by financial or secondary gain (even though there is not a shred of evidence to support such a claim), and that their claims for state benefits are unjustified

- Any negative characteristics of a minority of patients are typically generalised and ascribed to ***all*** ME/CFS patients, without any supportive evidence

- Deniers suggest or imply that patients have formidable powers, for instance that they are able to influence certain institutions; that they get the media on their side and even that they have managed to influence the World Health Organisation. It is also alleged that patients use such tactics to misrepresent the situation to lead others astray

- Deniers even re-write medical history and alter it so that it appears to support their own claims (this is certainly demonstrable in the psychiatric interpretation of the ME literature)

- Deniers may attempt to rename or reclassify the condition (for example claiming it as a modern form of an old (psychiatric) illness)

- Deniers make inappropriate comparisons between syndromes, suggesting that they are all simply the same (psychiatric) syndrome, ignoring or downplaying any specific and / or unusual features which are present.

In the case of ME/CFS, it seems irrefutable that the tactics of denial which were exposed in the Channel Four programme mentioned above are indeed being implemented by the psychiatrists of the Wessely School; out of the many available illustrations, just the following are provided:

- On 25th April 2000, Dr Michael Sharpe of Edinburgh wrote a letter to Mrs Ann Crocker in which he stated *"I understand your desire to have the condition classified as a Neurological Disorder (but) trying to change doctor's* (sic) *behaviour by altering classification probably will not work and might even provoke a paradoxical response".* The reality is that ME is already formally classified by the World Health Organisation in the ICD as a neurological disorder, and it is Wessely School psychiatrists (not patients) who are actively trying to "alter the classification" ***from*** neurological ***to*** psychiatric.

- On 18th January 2000 Simon Wessely wrote to the Countess of Mar that the *"ad hominen* (sic) *attacks"* upon him *"may have the unforeseen outcome of re-inforcing unhelpful stereotypes of sufferers held by some in high office".* Again, this seems to be nothing less than a threat, with the use of an intimidation technique made, it must never be forgotten, to very sick human beings who have been trying since Wessely came to such prominence in 1987 to redress the wrongs perpetrated upon them by these powerful medical deniers.

APPENDIX VIII: Two FINE Trial Case Histories

It is notable that an FOIA request made in 2005 for a copy of the FINE Trial Manual to The University of Manchester was refused (the Fatigue Intervention by Nurses Evaluation Trial was a concurrent trial to the PACE Trial). **One of the grounds of refusal was that access to the Manuals might be a mental health risk to patients who were not trial participants**. By letter dated 24th June 2005, Alan Carter of The Directorate of Corporate Services wrote to the applicant and his reply speaks for itself:

"We have considered the status of these manuals at length and have come to the following decision in this case…The University has decided not to disclose this material under the following exemptions in the Act:

" 1. Section 38 (Health and Safety). 'Information is exempt if its disclosure under this Act would, or would be likely to endanger the physical or mental health of any individual'. ***The team consider that putting these documents into the public domain would give rise to the risk that patients would endeavour to treat themselves using it.***

" 2. Section 43 (Commercial Interests). 'Information is exempt information if its disclosure under the Act would, or would be likely to, prejudice the commercial interests of any person (including the public authority holding it). There are two aspects to the application of this exemption. ***Firstly, if the treatments under investigation in this Trial are successful, The University of Manchester would wish to develop training packages for use by PCTs (Primary Care Trusts). The trial team feel that the development of these packages would be compromised if the manuals were put into the public domain prior to this development.*** *Secondly, if the patient manuals were put into the public domain whilst the Trial was still in progress, the trial team feel that this could lead to cross contamination of the results.* ***This would endanger the University's commercial interests in developing treatment packages as detailed above****, as well as endangering completion of the Trial.*

"The University has concluded that whilst there is a significant public interest in the treatment of CFS/ME, ***this is outweighed both by the public interest in preventing mental health risks to patients****, and the long term public interest in ensuring that potentially valuable research into treatment can be completed and utilised successfully".*

For the University of Manchester to suggest that access by non-participants to the FINE Trial Manuals might be a mental health risk seems absurd, since the University's own position is that the Manuals can only be of benefit.

Two FINE Trial Case Histories

There can be little doubt that some patients on both the PACE and FINE Trials think they are being coerced, bullied and harassed: participants in both trials have provided evidence of this. One person who withdrew from the PACE Trial reported that she was harassed by the therapist, who repeatedly exerted pressure on her not to withdraw from the trial and who was hostile and very angry and defensive when she refused to give in to his coercion. His behaviour was likened to that of a car salesman and it was obvious that he was more concerned about keeping his numbers up and that pressure was being put upon him to do so.

That patients are bullied into aerobic exercise (which can be detrimental to people with ME/CFS) is illustrated by two case histories.

Miss D

Miss D has been ill for 17 years with ME/CFS. In February 2007, when her condition was moderate in severity, she agreed to take part in the exercise element of the FINE trial. Before taking part, Miss D was optimistic as she was told that that there was an 80% success rate with this exercise intervention for her condition.

After being assessed, Miss D was encouraged, with support from the nursing staff, to exercise and to keep exercising although she felt she could do no more. She was encouraged to continue regardless, even though her health was deteriorating.

Miss D experienced a downward spiral in her physical health and was completely overwhelmed with fatigue and physical pain. In hindsight, she wished she had stopped; however, she continued in good faith believing that she would get better if she complied with the demands of the trial.

Miss D also has a stomach ulcer. Before the trial this was a mild condition and was under control. The increased stress of the physical exercise that she was required to do made her stomach ulcer worse until one day when she was attending her GP's surgery, her ulcer ruptured. Miss D was rushed to hospital and was given 8 pints of blood. She remained in hospital for 3 weeks to be monitored and for her to recover. She nearly died and was lucky that she was in her GP's surgery when this rupture occurred.

Before starting the trial, Miss D rated her level of illness at between 5 and 7 out of 10. After the trial, she rated herself at 1 out of 10. She stated to the nurse carrying out the end of trial assessment that she was much worse; however, she feels that the severity of her deterioration in health was not fully acknowledged in the final report. She felt misrepresented. This was easy to do as Miss D was vulnerable and was not in a position to be forceful and to correct or alter the final report. She felt the final report had a positive spin to it that was not congruent with her feelings or experience.

21 months after the trial Miss D now rates her health to be 3 to 4 out of 10 and she is still not back to where she was before taking part in it. Looking back, Miss D wishes she had researched what was being proposed more thoroughly and bitterly regrets having taken part. It very nearly killed her.

In summary, Miss D has come to recognise through bitter experience that vulnerable people who are willing to do almost anything to help themselves get better are easily persuaded into doing things which are detrimental to their health. She feels misled about the claimed 80% success rate. She would like to know why she was misled and where the evidence for this 80% success rate is.

She strongly recommends those with ME say no to this type of intervention.

Miss C

Miss C, aged 39, contracted what was thought to be viral meningitis in 2002 from which she never recovered. She was diagnosed with ME/CFS. In 2004, she was asked to become a participant in the FINE Trial through Manchester University. She was sent literature about the effects of deconditioning in ME/CFS.

It was convincing and thorough and, based on the literature, Miss C made the decision to take part in the trial. At the start of the programme, Miss C defined her condition as being between 6 to 7 out of 10.

A nurse visited Miss C at home and she was given a series of aerobic exercises to complete daily. The exercises largely involved walking, step aerobics done outside and other aerobics to be completed indoors. After the initial visits the programme was administered via the telephone.

Initially Miss C made some minor improvement and persevered with the programme.

After the first month, she started to decline. Her symptoms increased in severity as the intensity and amount of exercise was increased. She reported this to the FINE team but was encouraged to continue even though she reported feeling unwell and that she was declining. She experienced an exacerbation of her gastrointestinal symptoms, which she was instructed to ignore and to continue with increasing the exercise time and intensity.

After four months, Miss C's health had deteriorated to the point where she could no longer continue to keep up with the programme.

Her condition continued to decline. At this point she was very weak, her symptoms were severe and she had to spend three months in bed. This was reported to the FINE Trial team. Miss C reports that they were not interested in her deterioration.

She was told that she had finished the trial and that she was considered a success and to be cured due to her initial improvement.

This was distressing for Miss C as this was clearly not the case. It was the opposite of what she was reporting to the FINE team. She felt that she was not being listened to. At the end of the trial there was no follow-up care and all the counselling and support that was available during the trial was withdrawn. Miss C describes this withdrawal as profoundly disturbing. She could not understand the silence and the lack of interest in her worsened condition. As a professional herself, she considers this to be unethical. She has been too ill to consider making a complaint about her treatment.

Since undertaking the graded exercise, Miss C now rates her condition to be 2 out of 10 and she continues to decline. She now has added disabilities that were exacerbated by the graded exercise regime.

She hopes that others have not been bullied in the same manner.

In summary, it cannot be emphasised enough that these case histories are believed to be but the tip of the iceberg; certainly it seems that there may have been research malpractice and outright scientific misconduct, and the bullying experienced by Miss C accords with the undue coercion experienced by the PACE Trial participant referred to in Section 3 above who expressed her dismay at the involvement of Action for ME with the trial.

Appendix IX: International Clinical and Research Conferences on ME/CFS

In 2006 it was announced that the combined MRC / AfME "Summit" had been re-convened for November 2006 (Co-Cure NOT: Research Summit – AfME (UK) 14th September 2006); the announcement stated: *"As far as we know, this will be the first time that neurologists, immunologists, pain and sleep disorder specialists, epidemiological psychiatrists, pathophysiologists and others will work together to explore innovative ways of tackling ME"*

In their article "Incessant Belief" of September 2006 (http://www.meactionuk.org.uk/Incessant_belief.htm), Marshall and Williams drew attention to the misinformation contained in that announcement and to what seemed to be a disturbing lack of scientific rigour on the part of the MRC in relation to ME/CFS issues, noting that high scientific standards seem sadly lacking when it comes to funding research into ME/CFS:

"In a recent letter from Heather Finch of the Medical Research Council's Knowledge and Management Group, the MRC repeated its well-worn mantra about "high quality" research: "research excellence will continue to be the primary consideration in funding decisions" (see Co-Cure EDU: 16th September 2006). Of interest is the fact that Ms Finch also stated: "Awards *may* be made according to their scientific quality". "*May*" be made according to their scientific quality? Why not "*are*" made according to scientific quality?

"We have previously noted what seems to be a disturbing lack of scientific rigour on the part of the MRC in relation to ME/CFS issues and have noted that high scientific standards seem sadly lacking when it comes to funding research into ME/CFS: see, for example the following:

(1) "**Some questions about ME/CFS to which credible answers are urgently required"** (22nd March 2004) http://www.meactionuk.org.uk/Some_Questions_-_220304.htm

(2) **"Questions for the MRC"** (18th June 2005)
http://www.meactionuk.org.uk/Question_for_the_MRC.htm

(3) "**Issues re the use of the Oxford criteria for the MRC 'CFS' Trials**" (20th June 2004)
http://www.meactionuk.org.uk/SIGNS_in_ME.htm

(4) "**ME/CFS and Fibromyalgia: additional considerations for the MRC in relation to the PACE trials"** http://www.meactionuk.org.uk/Additional_considerations_re_MECFS_and_FM.htm

(5) "**High Standards at the MRC?**" (21st April 2005)
http://www.meactionuk.org.uk/High_Standards_at_the_MRC.htm

(6) **"ME Exists: True or False?"** (18th August 2006)
http://www.meactionuk.org.uk/ME_Exists_-_True_or_False.htm

Given its track record, especially the findings in the Report of the House of Commons Science and Technology Select Committee that under the Chairmanship of Dr Ian Gibson MP was excoriatingly critical of the MRC (see The Work of the Medical Research Council: Third Report of Session 2002-2003 / HC132, March 2003), how can the MRC credibly continue to assert that the PACE CFS trial meets the stringent and rigorous criteria that it claims to require?

It has just been announced that the combined MRC / AfME "Summit" has been re-convened for November 2006 (see Co-Cure NOT: Research Summit – AfME (UK) 14th September 2006); the announcement states: *"As far as we know, this will be the first time that neurologists, immunologists, pain and sleep disorder specialists, epidemiological psychiatrists, pathophysiologists and others will work together to explore innovative ways of tackling ME".*

What an extraordinary claim: why have the MRC and AfME ignored all the international Clinical and Research conferences on ME/CFS since 1988, many of which were reported in AfME's own magazine?

Have the MRC and AfME forgotten the US NIAID (National Institute of Allergy and Infectious Diseases) Symposium held at the University of Pittsburgh in September 1988; the Rhode Island Symposium in 1988; the Rome Symposium in 1988; the San Francisco conference in April 1989; the British Post-Graduate Medical Federation Conference in London in June 1989; the Los Angeles International Conference in February 1990; the First World Symposium held in 1990 at Cambridge University, UK; the Charlotte Research Conference in November 1990; the Canadian Workshop at the University of British Columbia, Vancouver, in May 1991; the Dublin International Symposium in May 1994 (held under the auspices of The World Federation of Neurology); the First World Congress (also under the auspices of The World Federation of Neurology) in Brussels in 1995; the Second World Congress in Brussels in September 1999; the Bloomington Conference in Minnesota in October 2001, and the International Clinical and Scientific Meetings presented by the Alison Hunter Memorial Foundation in Australia, especially the Third International Meeting in Sydney in December 2001?

Have the MRC and AfME forgotten the biennial International Research and Clinical Conferences hosted by the American Association of CFS (AACFS, now the IACFS / International Association of CFS), including the Albany, New York, conference in October 1992; the Fort Lauderdale, Florida, conference in October 1994; the San Francisco conference in October 1996; the Boston, Massachusetts, conference in October 1998; the Seattle conference in January 2001; the Chantilly, Virginia (Washington D.C.) conference in January – February 2003; the Madison, Wisconsin, conference in October 2004?

Are the MRC and AfME aware of the forthcoming IACFS Professional Research Conference that is to be held at Fort Lauderdale in January 2007? Will they be sending representatives?

Have the MRC and AfME forgotten the Scientific Workshops such as the one co-sponsored by the US National Institutes of Health in June 2003 on neuro-immune mechanisms in (ME)CFS and the two MERGE workshops (including the Royal Society of Edinburgh funded Workshop in 2003 and the MERUK Colloquium in July 2006), which consisted of presentations by key scientists with a working knowledge of ME/CFS, the aim being to facilitate links between scientists working towards the common goal of understanding the biomedical basis of ME/CFS?

The above lists are by no means comprehensive, so it is absurd for the MRC and AfME to appear to believe that their "Summit" represents the first time that researchers have collaborated "*to explore innovative ways of tackling ME".*

How can it be "high quality" science to ignore the evidence that was presented at these international meetings over the last 18 years?

All this has been pointed out many times before, yet the MRC and the psychiatrists it so favours continue to ignore the evidence".

<u>Books on ME/CFS</u>

Since 1938, there have been thousands of published papers in the medical literature that document biological abnormalities in ME/ICD-CFS and there are also many books, both self-help and medical textbooks, some of the best – in addition to Osler's Web by Hillary Johnson, Crown Publishers Inc, new York, 1996) which is essential reading -- being (1) The Clinical and Scientific Basis of Myalgic Encephalomyelitis Chronic Fatigue Syndrome; edited by Byron M Hyde, Jay Goldstein and Paul Levine, published by The Nightingale Research Foundation, Ottawa, 1992; (2) Myalgic Encephalomyelitis; Celia Wookey; published by Croom Helm Ltd 1986; reprinted 1988 and 1989, Chapman and Hall Ltd (this book

provides numerous case histories that cannot be bettered as teaching material; (3) Postviral Fatigue Syndrome; A Melvin Ramsay; published by Gower Medical Publishing, London, 1986; reprinted as Myalgic Encephalomyelitis and Postviral Fatigue States; Gower Medical Publishing, London, 1988 (recently re-issued by the UK ME Association); (4) The Disease of a Thousand Names: Chronic Fatigue / Immune Dysfunction Syndrome; David S Bell; published by Pollard Publications, Lyndonville, New York 1991; (5)) Post-Viral Fatigue Syndrome; edited by Rachel Jenkins and James Mowbray; published by John Wiley & Sons, Chichester 1991; (6) Chronic Fatigue Syndrome and the Body's Immune Defense System; Roberto Patarca-Montero; published by Haworth Medical Press, 2002; (7) Chronic Fatigue Syndrome – A Biological Approach; edited by Patrick Englebienne and Kenny de Meirleir; published by CRC Press, 2002.

No-one who is aware of this wealth of information can credibly doubt the reality, the validity and the devastation of this organic multi-system disease.

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