Background information and illustrations of evidence that CBT cannot improve ME/CFS which NICE disregarded

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Executive Summary

This document looks in particular at cognitive behavioural therapy (CBT) which, together with graded exercise therapy (GET), is the only management intervention recommended by NICE in its Guideline CG53 on "CFS/ME" of 22nd August 2007. This is in spite of the fact that these interventions have been shown to be at best unhelpful to those suffering from ME/CFS, and is in defiance of the substantial body of scientific and biomedical evidence regarding ME/CFS, evidence which the NICE Guideline Development Group (GDG) ignored.

This document also seeks to provide further supportive background information concerning the nature of ME/CFS, including the fact that it can for some be a fatal condition. This information was also ignored by the GDG.

The key points can be summarised as follows:

(i) Background Information

- Myalgic Encephalomyelitis (ME) has been formally classified by the World Health Organisation as a neurological disease since 1969. In 1992 the WHO approved the term "chronic fatigue syndrome" (CFS) as a term by which ME may be known, hence the term "ME/CFS" is used to denote the disorder
- The Guideline Development Group (GDG) was directed to subsume the distinct disorder ME/CFS within the label "CFS/ME" that encompasses a wide-ranging group of patients who suffer from a "primary complaint of fatigue for six months or more" and includes those with somatoform psychiatric disorders
- ME/CFS and "CFS/ME" are not the same condition
- The focus by the GDG on simply "chronic fatigue" is in defiance of all the biochemical abnormalities that have been shown to exist in ME/CFS patients
- The GDG does not explain how its recommended psychotherapy management regimes of cognitive behavioural therapy and graded exercise therapy (CBT/GET) can restore the damaged genes, nervous system, cardiovascular, immune, digestive and endocrine system of ME/CFS patients
- Members of the GDG were specifically directed not to consider the total evidence-base on ME/CFS in the production of the Guideline. NICE therefore failed in its remit to produce a Guideline to aid diagnosis
- The focus on the psychosocial model of ME/CFS brings disrepute on those who perpetuate it, including NICE, who give no credible reason for disregarding so much relevant scientific and biomedical evidence
- An explanation for the denial and suppression of such a large body of evidence is the vested interests of those who have gained materially from continuing such suppression and denial
- ME/CFS can cause death; "CFS/ME" does not. UK Coroners are now providing incontrovertible statements that ME/CFS can lead to death, something that the ME community has known for many years. However, deaths from ME/CFS due to end-organ failure are usually recorded as such, without the underlying ME/CFS being mentioned on the death certificate
- Significant and distressing social isolation is very common in people with ME/CFS, leading to increased and unnecessary suffering; there are many tragic case histories.

(ii) **Illustrations of evidence about ME/CFS that NICE ignored**

- There can be no dispute that there is a substantial body of evidence showing that ME/CFS is not a somatoform disorder and should not therefore be managed as such as recommended by the NICE Guideline
- "ME/CFS is associated with physical, psychological and social distress (and) cannot be defined using just one of these dimensions"
- "Wessely's work on depression and CFS is methodologically flawed"
- "Excessive physical exertion will exacerbate CFS symptoms and may worsen the course and prognosis"
- "Cognitive behavioural intervention studies conducted in Australia and the United States have not found significant improvements in functioning or symptoms"
- "Not only do patients with severe (ME)CFS not recover to full health, they remain quite severely ill for many years"
- The Oxford criteria for "CFS" (created and used by the Wessely School) specifically include patients with primary psychiatric diagnoses
- The symptoms of ME/CFS occur in multiple organ systems and no other disorder can account for them
- "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".

(iii) **Evidence that CBT is ineffective**

- The Guideline recommends CBT/GET for all patients in the UK with "CFS/ME", and states that this includes those with ME/CFS
- Not only did NICE ignore the fact that the recommended interventions (CBT/GET) are not effective, it ignored the evidence that subsuming all states of "chronic fatigue" into one functional somatic syndrome is contra-indicated, as well as evidence that most of the randomised controlled trials (RCTs) on CBT on which the GDG relied are seriously flawed
- In most of the ten trials of CBT upon which the GDG relied, the methodology does not meet even the most minimally acceptable standards
- The trials used give a total of 480 patients out of an alleged UK total of 240,000 patients and is insufficient data upon which to recommend a national strategy
- Patients with pre-existing psychiatric co-morbidity were not excluded from the studies relied upon
- Nowhere is there any evidence that patients fully recovered
- The behavioural model of "CFS/ME" offers relatively little; it is supported only by researchers with a professional interest in psychosocial aspects of illness. This model dominates the NICE management regime
- There is no credible evidence to support the GDG's claim that the best practice evidence-base is the nationwide implementation of CBT/GET for patients with "CFS/ME".

(iv) **Conclusion**

- A basic question never addressed by those who favour the psychosocial model of "CFS/ME" is: if patients are not cured by psychotherapy (which its proponents concede), then what is it that they are not cured from?
- Why does the NICE Guideline recommend only psychosocial therapy for "CFS/ME" (which is said to include ME/CFS) that has been clearly shown not to be effective?

Background information and illustrations of evidence that CBT cannot improve ME/CFS which NICE disregarded

An article in The Times on 21st July 2008 about the National Institute for Health and Clinical Excellence (NICE) made a clear statement: "***When (NICE) gives bad advice, people suffer***".

In relation to its recommended management regime for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), NICE has given bad advice in its Clinical Guideline 53 of 22nd August 2007 (Chronic Fatigue Syndrome / Myaglic Encephalomyelitis (or Encephalopathy): diagnosis and management of CFS/ME in adults and children). Unless that Guideline is revoked and replaced by an accurate and well-informed Guideline, people with ME/CFS will continue to suffer.

Of prime importance in relation to any legal challenge to the NICE Guideline CG53 on "CFS/ME" is the fact that, in defiance of the evidence that myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) is a classified nosological entity, the Guideline Development Group (GDG) was directed to subsume this distinct disorder within the contrived and heterogeneous label "CFS/ME", a label that does not denote people with ME/CFS but which encompasses a wide-ranging group of patients who suffer from "*a primary complaint of fatigue for six months or more*" and which specifically includes those with somatoform psychiatric disorders.

The deliberate blurring of the distinctions between chronic fatigue, CFS/ME and ME/CFS means that those with ME/CFS will continue to receive a psychiatric diagnosis. This unjustified subsuming of any state of "chronic fatigue" into one single somatoform disorder (CFS/ME) has led, and will continue to lead, to inappropriate management strategies which may be potentially fatal for some people with ME/CFS.

ME has been formally recognised as a neurological disease by the World Health Organisation since 1969. It was described clearly and cogently by Dr Melvin Ramsay of The Royal Free Hospital in London, who was regarded as the Father of ME from his long clinical experience of it (Postviral Fatigue Syndrome. Gower Medical Publishing, 1986; the second edition was entitled Myalgic Encephalomyelitis and Postviral Fatigue States, Gower Medical Publishing, 1988. Ramsay told many people that he always regretted allowing himself to be persuaded not to use the term ME in the title of the first edition and insisted on using it in the second edition).

There is substantial evidence that, even though NICE asserts they are the same condition, ME/CFS is not the same as "CFS/ME" – this is mere opinion held and promoted by psychiatrists of the Wessely School that, in the UK, has been elevated to the status of medical certainty in defiance of and contrary to established scientific evidence. Even if the Wessely School psychiatrists believe in their own myth that there is no such distinct disorder as ME/CFS, their unproven beliefs should not be accorded preference over the medical science that has shown them to be wrong.

By deliberately ignoring the published evidence about the nature of ME/CFS and by supporting the Wessely School hypothesis that it is a behavioural disorder, the NICE Guideline has contributed to the misinformation regarding every aspect of ME/CFS that is propagated by these psychiatrists.

To focus on the single symptom of "chronic fatigue" in its management recommendations that NICE asserts relate to people with ME/CFS, whilst down-playing so many other key symptoms of ME/CFS, and to ignore the evidence of acquired (i.e. not congenital) gene abnormalities in ME/CFS (in particular, clear evidence of prominent RNA not observed in normal controls, with the prominent RNA bands sequenced showing homology with human genes that are noted for the tendency for gene rearrangement under severe physiological stress) is to defy reality. This evidence of gene abnormalities that is found only in ME/CFS was presented at the American Association for Chronic Fatigue Syndrome (AACFS, now the International Association for ME/CFS) International Research Conference held in Seattle in January 2001 and was available to the GDG.

The GDG offers no explanation as to how cognitive behavioural therapy or graded exercise can restore defective genes. Indeed, no explanation or evidence is offered as to how CBT/GET is supposed to correct the damage that has been shown to occur in the central and autonomic nervous system, the cardiovascular system, the immune system, the endocrine system and the gastro-intestinal system of those with ME/CFS.

CBT and GET are based on the belief of their proponents that fear of activity is one of the reasons for continued disability in "CFS/ME" (Pesek J, Jason LA et al: Journal of Human Behaviour in the Social Environment: 2000:3:59-77).

Given the substantial published evidence that psychological factors do not contribute to the extreme illness and disability seen in ME/CFS, it is irrational for NICE to claim that psychological interventions such as CBT and GET contribute to improvements in physical functioning in those who wish to recover.

Nothing detracts from the fact that the Guideline recommends only psychotherapy for people with ME/CFS.

It is disingenuous for NICE to state that CBT is used in diseases such as cancer and heart disease, therefore patients with "CFS/ME" should not reject it on the grounds that it is a psychological intervention: the key difference is that in other medical disorders, CBT is offered as adjunctive therapy, not as the primary (and only) intervention as is the case with ME/CFS, where nothing else is on offer. This is akin to telling cancer sufferers that if they would only change the way they think about their illness, they will improve.

Misleadingly, the implied message of the NICE Guideline is that "CFS/ME" is a psychogenic disorder; unfortunately, UK doctors have a lamentable track record of dismissing and denigrating patients whom they believe to be the creators and perpetrators of their own ill-health, and the present Guideline will perpetuate this abuse.

It was in 1990 that Peter Wakeford wrote in the UK ME Association newsletter: "*Psychiatrists want the disease firmly in their domain. They're gathering even now like locusts to redefine it. I have phone calls from isolated desperate people who say: 'The psychiatrists are trying to put me away in an institution. They're taking away my day care. Help me'. It's appalling that even today, people I know are in psychiatric institutions – and they've got ME, which is an organic illness"* (Perspectives, Summer 1990; pp 25-27).

A decade later, in 2000 Gwynneth Elias commented in despair at the lack of respect and care afforded to those with ME/CFS. She was a patient at the "CFS" clinic at one of the London Teaching Hospitals and was told by the doctor that she should not be afraid to increase her activity, and that she needed to adopt a positive attitude in order to improve: "*The arrogance of their assumptions was truly staggering. I was utterly devastated by the lack of help and courtesy. I was disempowered and tempted to withdraw back into the isolation of the illness, as most before me have done. Less than 5% of those in my local support group see a Consultant; most exist with no support*" (Perspectives, January 2000:30).

As Erik Johnson pointed out in the eBMJ in 2004 about inappropriate psychiatric interventions for ME/CFS: " *psychological theorists deliberately disregard or manipulate in an imprudent manner (the evidence) if it jeopardises their conceptual model of the illness or diminishes their influence in its treatment"* (eBMJ: 15th July 2004).

Numerous surveys have shown that NHS provision is not addressing the needs of those with ME/CFS (for example, the York & Ryedale ME support group's survey of 2001, as reported in Perspectives 2001; Autumn:15).

By implying – by recommending only psychotherapy -- that ME/CFS is a psychosomatic problem, the NICE Guideline has done nothing to correct or even alleviate the situation. Commenting on a GMTV interview with the Welfare Minister James Purnell on 21st July 2008 about the increased difficulties people with ME/CFS will be likely to experience in obtaining and maintaining State benefits, Sir Peter Spencer,

Chief Executive of the charity Action for ME, said: "*This creates additional stress which adds to the problems which people already face. It also demonstrates that government departments still fail to understand the clinical realities of ME*" (LocalME@yahoogroups.com).

The GDG was directed to ignore the urgent need to subgroup "CFS/ME"

It has now been confirmed by a member of the GDG that members were specifically directed not to consider the total evidence-base on ME/CFS in the production of the Guideline (J.Infection 2007:55:6:569-571). Such a direction ensured that the GDG failed in its remit to produce a Guideline to aid diagnosis.

There is abundant evidence in the literature of calls to distinguish between individuals with different causes of their fatigue. For example, in 1999 US researchers Professor Leonard Jason et al highlighted such a need:

"One consequence of such patient heterogeneity is that when patients groups are combined, distinctions between individuals with different causes of their fatigue, or different syndromes, are blurred. ***For years, investigators have noted many biological abnormalities among patients with (ME)CFS, including over-activated immune systems, biochemical dysregulation in the 2-5A synthetase/RNase L pathway, cardiac dysfunction, EEG abnormalities, abnormalities in cerebral white matter, decreases in blood flow throughout the brain, and autonomic nervous system dysfunction. Lack of consistency in laboratory findings might be a function of combining patients into a large heterogeneous group rather than analysing them within sub-groups****. To complicate matters further, individuals with (ME)CFS experience different phases of their illness"* (JCFS 1999:5:3-33).

By intentionally disregarding the existing evidence-base of published knowledge about ME/CFS and by focusing on only a few methodologically flawed randomised controlled trials (RCTs) in its Guideline on "CFS/ME", and by relying only on those flawed RCTs for its recommendation of the psychological interventions cognitive behavioural therapy and graded exercise therapy (CBT/GET) as the primary management intervention, **NICE has compounded the erroneous view that ME/CFS is a primary psychosomatic disorder.**

No-one disputes that, as with virtually all serious and chronically disabling diseases, there may be accompanying psychological problems. However, this is very different from asserting that a disorder is a primary behavioural disorder and must be managed as such, as has been the case with ME/CFS in the UK for the last two decades.

The deliberate ignoring by the GDG of the sheer volume of 70 years' published evidence that ME/CFS is not a primary behavioural disorder raises important questions, particularly the question as to why such evidence should continue to be ignored by agencies of the State such as NICE, and why the focus of management should be so resolutely centred on changing ME/CFS patients' rightful belief that they suffer from a devastating organic disorder to the acceptance that their disorder is psychosomatic (a compulsory requirement if people with ME/CFS wish their State benefits to continue, since they are required to undertake "rehabilitation" programmes).

The denial of the nature of ME/CFS by the Wessely School (and thus by NICE)

The denial of medical science in relation to ME/CFS gained momentum in 1987 with the advent of psychiatrists of the Wessely School and has continued unabated, as has their well-documented involvement with the medical insurance industry.

The Wessely School members have been prodigious in proselytising their belief that "CFS" (they did not routinely refer to it as "CFS/ME" until early 2002) is a psychiatric (behavioural) disorder, not only in the

mainstream medical journals but in the medical trade magazines such as "PULSE" and "GP", which have a much larger circulation and readership, being read by virtually every registered doctor in the UK.

For example, in June 1998 psychiatrist Peter White (now an influential lead adviser on "CFS/ME" to the Department for Work & Pensions) advised all UK doctors that exercise helps "CFS" and that: "*Most patients with CFS will also have a psychiatric disorder*". White stated that increasing exercise is important, "*aiming at a total of half an hour of exercise, five days a week"*. He continued: "*cognitive behavioural therapy has already been shown to be a useful treatment for patients with the chronic fatigue syndrome and can particularly help to challenge unhelpful illness beliefs and coping strategies"* (PULSE: 20th June 1998:86-88).

It was in 1998 that Professor Michael Sharpe, a psychiatrist who, with Wessely and White, is known to be heavily involved with the medical insurance industry and a key player in the Wessely School team of mental health professionals that is dedicated to "eradicating" ME and subsuming it within the heterogeneous "chronic fatigue" label, crystallised their intended approach:

"Cognitive behavioural therapy offers patients (with CFS/ME) a new way to think about their illness. ***The first application of CBT to chronic fatigue syndrome was by Wessely and colleagues (who proposed) a vicious circle model of the perpetuation of chronic fatigue whereby patients' beliefs about the illness lead to avoidance of activity and thus to chronic disability. Our group (i.e. the Wessely School) wanted to develop the behavioural approach. CBT helps patients to re-evaluate their beliefs (and) encourages them to change their behaviour. Change in the belief is an important factor in recovery.*** *The trials of CBT have shown that 'psychological' treatment is effective in patients with CFS"* (Cognitive Behaviour Therapy. Michael Sharpe. In: A Research Portfolio on Chronic Fatigue. Ed: Robin Fox. Published by The Royal Society of Medicine for The Linbury Trust, 1998).

In 2001, a short biography of psychiatrist Peter White stated: "*The first claim for Permanent Health Insurance (income protection) because of CFS or ME arose around 1987. CFS/ME is now one of the four commonest reasons for claiming income protection. Poor prognosis with CFS/ME has been found to be precipitated by certain illness beliefs and receiving a disability pension"* (Insurance Medicine, 3rd July 2001).

In 2002, Sharpe was equally clear: *"Functional symptoms are not going to go away. However, the form they take is likely to change****. 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 orientated and privatised doctors will collude with the patient's views that they have a disabling and permanent illness. It will be imperative that health and social policy address this problem. Funding of rehabilitation by commercial bodies has begun in the UK with organisations such as PRISMA and is likely to continue. Both health services and insurers now need to take a more positive approach"* (Functional Symptoms and Syndromes: Recent Developments. In: Trends in Health and Disability 2002, Report of UNUM Provident Insurance Company. Michael Sharpe).

The confirmation by Sharpe that CBT -- also known as "rehabilitation programmes" in an attempt to sell CBT to patients -- is being provided in the NHS by the company PRISMA is of particular interest.

PRISMA stands for "Providing Innovative Service Models and Assessments". It is based in Germany and is a multi-national healthcare company working with medical insurance companies. It arranges "rehabilitation" programmes and its recommended management is CBT. PRISMA claims to be especially concerned with long-term disability from the perspective of government, service providers and insurance companies. It claims to have developed a *"unique treatment programme"* for *"hopeless*" cases (it specifically includes those with CFS), claiming that such patients "*avoid physical exercise and social activities, as they fear these may trigger new bouts of complaints"*. In the PRISMA Company Information, Professor Simon Wessely is listed as a Corporate Officer. He is a member of the Supervisory Board. In order of seniority, he is higher than the Board of Management. He is listed as a *"world expert"* in the field of "*medically unexplained illnesses including Chronic Fatigue Syndrome"* (PRISMA Company Information, 2001).

Concern has been repeatedly raised that Wessely is recommending an NHS management programme for people with ME/CFS that is known to be potentially harmful but which is provided by a company of whose Supervisory Board he is a member.

The relentless focus on the unproven psychosocial model of ME/CFS brings disrepute on those who perpetuate it, including NICE.

NICE provides no credible reason for such blatant disregard of the relevant evidence.

It is completely unacceptable that the unsubstantiated personal beliefs of a few immensely influential psychiatrists with indisputable vested interests (i.e. the Wessely School) should continue to indoctrinate UK medicine regarding ME/CFS.

The matter of possible scientific misconduct by Wessely in his selection and presentation of the available evidence relating to ME/CFS was first raised in public in 1994 (see: The CFIDS Chronicle, Spring 1994:14-18). It is now time that he and his like-minded colleagues be held accountable for their published beliefs about ME/CFS and for the consequences of those beliefs upon many thousands of sick people suffering from a well-established organic disease, including the prevention of informed medical understanding and the loss of the provision of appropriate and compassionate care.

The most likely explanation for decades of denial and suppression of such a large body of scientific and biomedical evidence is the vested interests of all those who have gained materially from such continuing denial and suppression.

There is, however, an alternative explanation: that the phenomenal increase in cases of ME/CFS since the 1980s is linked to unavoidable daily exposure to a multiplicity of chemicals or even to chemical warfare agents. Indeed, a link to chemical warfare agents has been established (see below).

The cost implications for the NHS of providing suitable medical care and respite services for an increasing number of ME/CFS sufferers are enormous, as well as for the medical insurance industry to whom the Wessely School psychiatrists are consultant medical advisers (see, for example, www.meactionuk.org.uk/Notes_on_the_Insurance_issue_in_ME.htm). These same psychiatrists are also advisers to NICE via the Systematic Review Team at the Centre for Reviews and Dissemination at York upon whose Systematic Review of the literature the GDG relied so heavily.

Key questions require urgent answers: why were members of the Chief Medical Officer's Working Group on "CFS/ME" which met from 1998 to 2002 threatened with the Official Secrets Act?

Why are Medical Research Council (MRC) files on ME/CFS locked away in the National Archive at Kew and remain inaccessible until 2023 under the thirty-year rule?

Why has the MRC repeatedly rejected so many well-designed studies of the biomedical aspects of ME/CFS and why does it continue to fund only psychiatric studies of CBT/GET for "CFS/ME"? At a meeting held on 15th July 2008 at the MRC, attended by the Medical Adviser to the ME Association, it was made clear that there is no realistic chance of the MRC providing ring-fenced money for ME/CFS research and that there is no realistic chance of the MRC commissioning biomedical research into the disorder, as was recommended in section 6.5 of the Chief Medical Officer's report of 2002.

Why is the UK Establishment so determined to disregard the international science and to deny the reality of the nature of ME/CFS, just as in the case of Gulf War Syndrome?

That NICE has chosen to continue the misguided suppression of the ever-mounting evidence of serious organic pathology that has been internationally demonstrated in ME/CFS in its Guideline CG53 unsurprisingly fuels speculation within the ME community.

Evidence has now emerged that this may not be idle speculation after all.

The possibility of chemical contamination was raised during a four day Judicial Review in July 2008 in the High Court in London that was looking into the adverse effects of pesticides (brought by Georgina Downs); when pressed by the Judge about the effects of pesticide exposure, Robert Jay QC, Counsel for the Defendant (DEFRA), conceded that it appears these effects are not adequately covered by the current risk assessment model.

In the High Court, reference was made to the suggestion within the Royal Commission on Environmental Pollution (RCEP) Report that causation of ME/CFS may have links with systemic, long-term exposure to such products (Crop Spraying and the Health of Residents and Bystanders. Sir Tom Blundell. HMSO. September 2005: http://www.rcep.org.uk/pesticides/Crop%20Spraying%20web.pdf). That Report states:

"*Chronic fatigue syndrome or myalgic encephalomyelitis is a complex disorder. Diverse factors have been proposed as contributing to pathogenesis, including exposure to toxins, pesticides and other chemicals (Komaroff et al: Annual Reviews of Medicine 1998:49:1-13). Currently there are no animal models available to reflect all of the chronic ill health effects that have (been) associated with pesticide spraying, specifically multisystem, multisymptom disorders such as CFS. We are aware of some new animal models that reproduce some aspects of CFS that deserve further study. It is important to ensure that symptoms and syndromes that do not fit within traditional toxicological end-points are not ignored simply through lack of knowledge. This applies to the study of multisymptom illness".*

Mr Jay said it was the Defendant's position that no solid evidence existed to link exposure from any individual pesticide with (ME)CFS. Although not referring specifically to ME/CFS, the Judge (Collins J), was robust in his observation that if data and evidence are not routinely collected by the relevant authorities, how can the Government be so sure that causation does not exist?

Such a potential link does exist.

In 1999 **Professors Vojdani and Lapp from the US looked at the possible differentiation between virally-induced ME/CFS and chemically-induced ME/CFS and demonstrated that ME/CFS can be caused by viruses (as in the early epidemics) but also by chemicals** (Immunopharmacol Immunotoxicol 1999:21(2):175-202).

In December 2001, at the Alison Hunter Memorial Foundation International Conference on ME/CFS held in Sydney, Australia, Mohamed Abou-Donia, Professor of Pharmacology, Cancer Biology and Neurobiology, Department of Neurotoxicity, Duke University Medical Centre, Durham NC, demonstrated that stress can intensify the effects of relatively safe chemicals, making them very harmful to the brain and liver; even short-term exposure to chemicals, when combined with stress, is enough to cause wide-spread cellular damage (see, for example, Archives of Environmental Health 2003:58:8:484-497; Journal of Toxicology & Environmental Health 2004: February 27).

Significantly, it has long been known that the stress response is disordered in ME/CFS (see for example: Demitrack M et al; Journal of Clinical Endocrinology and Metabolism 1991:73:6:1224-1234; Crofford LJ and Demitrack MD; Rheum Dis Clin North America 1996:22:2:267-284).

In 2005, an important paper by Kaushik, Holgate, Kerr et al delivered a bombshell: this team studied gene expression in the blood of people with ME/CFS and found remarkable differences between patients and controls. Sixteen genes were identified as having an expression profile associated with ME/CFS. These genes can be grouped according to immune, neuronal, mitochondrial and other functions. **A neuronal component was identified that is associated with central nervous system hypomyelination, and the authors specifically noted the association of organophosphates and chemical warfare agents**. Further, the authors provided evidence of mitochondrial gene upregulation and observed: "*The upregulation identified may represent a common host response to persistent infection with several different viruses"* (Gene expression in peripheral blood mononuclear cells from patients with chronic fatigue syndrome. 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; Honorary Consultant Physician,

Southampton General Hospital, and a member of The Royal Commission on Environmental Pollution; his research interests include CFS.

Also in 2005, UK researcher Dr Derek Pheby, Co-ordinator of the UK ME Observatory, published Risk Factors for the Development of ME/CFS; this report states: "*Of possible risk factors, odds ratios greater than 2 were found for damaging initial treatment, and chemical exposure"* (JCFS 2005: [cover date 2004 / publication date 2005]:12:2:47-50).

ME/CFS causes death

People die from ME/CFS, but not from "CFS/ME".

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 prizewinner nominee) stated that there is **"a greater death rate than normals in the same age range"** (see: 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).

Perhaps the most tragic and well-known case 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) were 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 statements that ME/CFS can lead to death. This is something that the ME/CFS community has known for many years.

It was in 1957 that Dr Andrew Wallis reported the post-mortem histopathology on a female from Cumbria who had died of ME/CFS. The histopathology report (held at the University of Edinburgh) states:

> *"There are in the entire diencephalon, particularly around 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".*

It was indeed a significant finding and remains so, given the long history of vasculopathy in ME/CFS that abounds in the medical literature (which NICE entirely ignored): see, for example:

http://www.meactionuk.org.uk/Vade_MEcum.htm

http://www.meactionuk.org.uk/VASCULAR_PROBLEMS_IN_CFS.htm

http://www.meactionuk.org.uk/The_MRC_Profits_before_Patients.htm

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 postmortem 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 at the age of 32 and the death certificate of 19th June 2006 gives CFS as the cause of death, with acute renal failure (see below).

The most recent 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, there was evidence of severe inflammation throughout 75% of her spinal cord.

Evidence from 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 (chronic fatigue immune dysfunction, a commonly-used US term for ME/CFS) Foundation, 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).

Deaths from ME/CFS complications or end-organ failure such as myocarditis or pancreatitis or liver failure are usually recorded as such, without the underlying ME/CFS being mentioned on the death certificate.

Details of some ME/CFS deaths were presented to the UK Chief Medical Officer (CMO) in person by the Countess of Mar, Dr Elizabeth Dowsett (former President of the ME Association) and Doris Jones (an independent ME/CFS researcher) in March 1998 (The Organic Basis of ME/CFS. EG Dowsett, DM Jones, March 1998, available from DM Jones at cost price: 0208-554-3832).

These details were made available to the subsequent CMO's Working Group on "CFS/ME" but were ignored. It is a matter of record that five members of the Wessely School who were on the Working Group walked out just before the Report was published, refusing to endorse it because it did not categorically state that "CFS/ME" is a somatoform disorder. Those members were psychiatrists Professor Peter White, Dr Anthony Cleare and Professor Elena Garralda, behavioural nurse therapist Trudie Chalder (now a Professor at the Institute of Psychiatry) and Dr Alison Round, a public health physician who, in a paper co-authored with Dr William Hamilton (a member of the Guideline Development Group and Chief Medical Officer of a major medical insurance company for the past 15 years), concluded that in people who claim permanent health insurance for CFS, abnormal illness behaviour is of greater importance than previously recognised (JRCP 1998:32:1:44-48).

In the sample presented to the CMO, there were seven cases of cardiac failure, including two cases of cryptogenic myocardial fibrosis (as seen at the autopsy of Dr Eric Booth); four cases of cancer (incidence of which is known to be increased in ME/CFS patients: Levine et al, 1994: Clin Inf Dis 18: (Suppl 1):S49-S53; Johnson H, Osler's Webb 1996: Crown Publishers, New York; Levine et al. JCFS 1999:7:1; Levine et al 1998: Annals of Epidemiology: 8:(4):245-249), and cases of hepatic and renal failure. There are reports of hepatic and splenic involvement in ME/CFS going back to 1977 (for example: BMJ 1977:21 May:1350; Psychiatric Annals 1997:27:365-371; Rev Inf Dis 1991:13: (Suppl 1):S39-S44; J Psychosom Res 2000:48:59-68).

The GDG ignored all this evidence and recommended only behavioural interventions for such people.

Deaths directly implicating ME/CFS are mostly documented as suicide. This is not because patients are psychiatrically ill: it is because they are completely unable to look after themselves and are too sick to survive without the necessary social, medical and financial support which in the UK is consistently denied them due to the misinformation propagated about ME/CFS by the Wessely School.

Significant and distressing social isolation in people with ME/CFS is very common, leading to increased and unnecessary suffering; many case histories are tragic. People with ME/CFS have committed suicide when the intense and unremitting suffering and the battles with State agencies that they had to endure became unbearable.

A few illustrations (some of which were in the presentation to the CMO) are as follows:

- A young mother of two children in the west country was brusquely told by a nursing sister to pull herself together; severely sick with ME/CFS, she was driven to take her own life
- A young man aged 26 from Ireland went to England in search of treatment for ME/CFS; he returned to Ireland unimproved and took an overdose
- A mother of three children from Dublin asked her family what favourite meal they would like for their supper; she prepared it, then took a taxi to the coast and drowned herself because she could no longer endure the ravages of ME/CFS
- A young man with ME/CFS from Exeter tied a noose round his neck and attached the noose to a car, ending his life in a particularly gruesome way
- A man with ME/CFS from Worcestershire was so upset by the derogatory things written in his medical notes (which said he was a malingerer) that he killed himself
- An MP with ME/CFS (Gordon McMaster) killed himself by taking an overdose
- A young farmer with ME/CFS aged 31 died after taking an overdose of strychnine; he was found by his sister writhing in arched death throes
- A young man of 23 with ME/CFS killed himself by jumping into the River Ness in Scotland
- A young man with ME/CFS in Warwickshire hanged himself in the hallway of his home
- The wife of a Professor in South Wales committed suicide because of ME/CFS.

In 2001, Carli Berry from Yorkshire committed suicide on her 27th birthday.

Most recently, an inquest in May 2008 heard that a young man of 20 from Colchester, Essex, committed suicide after suffering from ME/CFS for ten years.

These serve only as illustrations; there are many more such tragedies.

From the information and statistics available to the ME Association (partly via a Press Cuttings service), the Medical Adviser is on public record as stating that there is about one ME/CFS suicide per month in the UK.

In 2006, in a study looking at the cause of death in ME/CFS, Jason et al stated:

"*(ME)CFS is a severe illness and it can affect virtually every major system of the body. Neurological, immunological, hormonal, gastrointestinal and musculoskeletal problems are all common among people with (ME)CFS.* ***The three leading causes of death in individuals with (ME)CFS were heart failure, suicide and cancer. The fact that approximately 20% of the sample died of heart failure is of importance given the growing evidence of cardiac problems among patients with (ME)CFS. Patients with (ME)CFS might have lower cardiac output, and the resulting low flow circulatory state could make it difficult for patients to meet the demands of everyday activity.*** *Given that (ME)CFS is one of the more common chronic health conditions, affecting potentially 0.42% of the population, it is imperative for international researchers and public health officials to seriously study factors that might influence functioning and mortality of those with this condition".*

Jason found that the age at which people with ME/CFS died was considerably younger than would have been expected in the general population (Causes of Death Amongst Patients with Chronic Fatigue Syndrome. Leonard Jason et al. Healthcare for Women International 2006:27:615-626).

A memorial list of some of the people who have died from ME/CFS is available: (http://www.ncf-net.org/memorial.htm).

Illustrations of evidence about ME/CFS that NICE chose to ignore

It is known that the selection of the Guideline Development Group members was carefully controlled and that NICE "*gave preference to those with day to day clinical experience for managing this condition"* (letter dated 23rd December 2004 from Nancy Turnbull, Chief Executive of the National Collaborating Centre for Primary Care to the Medical Adviser to the ME Association, rejecting his offer to be a member of the GDG. The letter says that the NCC-PC is funded "*to produce guidelines for the NHS by the National Institute for Clinical Excellence"*). This is evidence that only those already engaged in behavioural interventions were favoured as members of the GDG, since there is currently no other management of the disorder in the UK available on the NHS. This would seem to confirm the widely-held view that the GDG was specifically chosen to deliver a pre-determined outcome.

It should be noted that despite the published views of some members of the GDG, there is no evidence of maladaptive beliefs, nor of phobic avoidance of activity, in patients with ME/CFS, but there is evidence that the fatigue is not due to lack of motivation or effort. Longitudinal studies using appropriate measures have shown that patients' belief in a physical cause of their disease does not affect outcome; moreover, research indicates that a belief in a biological cause is not associated with poor mental health.

The alleged links between ME/CFS and psychiatric disorders reflect the overly-broad Oxford diagnostic criteria compiled by Wessely School psychiatrists and reflect these psychiatrists' choice of measures for assessing psychiatric morbidity.

There can be no dispute that there is a substantial body of evidence showing that ME/CFS is not a somatoform disorder and should not therefore be managed as a somatoform disorder as recommended by the NICE Guideline.

The illustrations that follow were all available to the GDG but were ignored.

In 1990, Australian researchers Hickie, Lloyd et al studied the pattern of "psychiatric" symptoms in a well-defined sample of patients with ME/CFS and found it to be compatible with that observed in other medical disorders. "*Patients were not excessively hypochondriacal. **Our results suggest that ME/CFS patients are no more psychologically disturbed before the onset of their illness than members of the general population**"* (British Journal of Psychiatry 1990:156:534-540).

In 1991, US surgeon Thomas English described his own experience of ME/CFS: "*There is nothing in your experience in medical school, residency, or practice with its gruelling hours and sleep deprivation that even approaches the fatigue you feel with this illness. I have talked with scores of fellow patients who went to our profession for help, but who came away humiliated, angry, and afraid. **The psychospeculation of their physicians was frightening and infuriating. It told them their doctors had little understanding of the real problem.** Many patients had lost careers, homes, families. There is nothing that you hold dear that this illness cannot take away from you. Nothing. **This is no illness for cookbook doctors. It is a disease for medical intellectuals with supple and open minds**"* (JAMA 1991:265:8:964).

In 1991, Yeomans and Conway concluded that: "*(ME)CFS is associated with physical, psychological and social distress (and) cannot be defined using just one of these dimensions".* Their study emphasised the ease with which psychiatric rating scales may lead to false positive diagnoses in patients with physical

symptoms and concluded: "***It is unnecessary and indeed unproductive to force patients into unsuitable diagnostic categories as a condition for treatment"*** (Journal of Infection 1991:23: (3):263-269).

In 1992, Nicole Phillips from Australia pointed out in the Australian and New Zealand Journal of Psychiatry: "*It is important for psychiatrists to be aware of the rapidly expanding body of new literature on this illness. Wessely's work on depression and CFS is methodologically flawed (because) the group of patients studied were those with 'a primary complaint of fatigue for six months or more'. They were not diagnosed using the full criteria and therefore included many 'non-pure' CFS cases.* ***The nature of the illness should be borne in mind when designing programmes with increasing levels of activity. Excessive physical exertion will exacerbate CFS symptoms and may worsen the course and prognosis.*** *Psychiatrists need to utilise terminology such as 'the sick role' and 'abnormal illness behaviour' with great caution when discussing chronic illness. Not only will they alienate their medical colleagues but, more importantly, the patients they are trying to help"* (Aust & NZ J Psychiatry 1992:26:329-330).

In 1995, Trigwell et al demonstrated that: "***Those who see CFS as primarily a psychiatric disorder regard it as a variety of somatisation. Scores on the illness behaviour questionnaire cannot be taken as evidence that chronic fatigue syndrome is a variety of abnormal illness behaviour, because the same profile occurs in multiple sclerosis****"* (BMJ 1995:311:15-18).

In 1996, US neurologist Ben 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 epidemiolgical 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 one 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 2000, Friedberg et al evaluated symptom patterns in patients with ME/CFS who had been ill for longer than 10 years; chemical sensitivities were assessed (these being a common feature of ME/CFS, which Wessely School psychiatrists ascribe to somatisation). Chemical sensitivity scores were significantly higher in the long-duration group. The authors found that: *"long-range coping behaviour stabilises well before 10 years of illness. (ME)CFS symptom severity scores were significantly correlated with measures of allergy symptom severity. Allergy, confirmed by allergy testing, was the most frequently reported medical condition (88.8%). Evidence for hypersensitivity was found. A hypersensitivity mechanism and viral infection may contribute to illness persistence in (ME)CFS"* (J Psychosom Res 2000:48:59-68).

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). It is noted that 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"* (a view that persists in the widely-publicised work of the Wessely School which has in principle been adopted by NICE by virtue of its management recommendations).

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

In 2006, Demitrack encapsulated the problem that NICE declined 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***". Commenting on clinical outcomes, Demitrack says: "*Our group has shown that the measurement error of rating scales can be enormous and can substantially undermine the presumed statistical power of the study".*

Demitrack concludes: "*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 (although possibly too late to have been considered by the GDG, had it been minded to do so, but 61 out of 64 references pre-date the Guideline, so were available to the GDG), 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 and NICE 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).

Despite the considerable amount of peer-reviewed international evidence that it is imperative to subgroup the heterogeneous condition "CFS", the GDG stated that there is no evidence to justify subgrouping (see below) and the Guideline recommends blanket behavioural management regimes for everyone (mildly, moderately and severely affected, and children and adolescents with "CFS/ME" in the UK.

The evidence that CBT is ineffective

Despite the placatory verbiage in the Guideline, the bottom line is that it recommends CBT/GET for all patients in the UK with "CFS/ME", and this includes those with distinct ME/CFS.

There is abundant evidence that CBT does not work, not only in ME/CFS but in general, yet this evidence was disregarded by the GDG (see for example: http://www.meactionuk.org.uk/Deliberate_deceit.htm and http://www.meactionuk.org.uk/EVIDENCE_OF_EFFICACY.htm).

Although post-dating the NICE Guideline on "CFS/ME", 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 £2.6 million awarded to the Wessely School psychiatrists by the MRC to support the claimed efficacy of CBT in "CFS/ME", 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 that definitely pre-dated the Guideline 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).

Not only did NICE ignore the evidence that the recommended interventions (CBT/GET) are not effective, it also ignored the evidence that subsuming all states of "chronic fatigue" into one functional somatic syndrome is contra-indicated, as well as the evidence that most of the RCTs on CBT on which the GDG relied are seriously flawed.

The GDG's "evidence-base"

The York Review of 2005 (which is the 488 page Appendix I to the Guideline that was written by Bagnall et al specifically to support the work of NICE) identified ten trials of CBT that were deemed suitable for inclusion in the Systematic Review. There were five RCTs of CBT, one controlled trial of CBT (Whitehead et al, 2002), and four studies of modified CBT (Cox 1999, Cox 2002, Friedberg 1994, Taylor 2004, which do not appear to have been fed into the recommendations).

In most of the ten identified trials of CBT, the methodology does not meet even the most minimally acceptable standards.

Somewhat carelessly, page 198 of the Full Guideline states at 6.3.3.1: "*Ten RCTs (sic) met the inclusion criteria for assessment of CBT or modified CBT in people diagnosed with CFS according to one of the recognised case definitions. Eight of the studies reported beneficial effects of CBT. Two studies with low validity scores showed no significant differences".*

Five out of the ten listed trials of CBT registered no overall effect (see Full Guideline, Appendix I [York Review 2005] page 94). If the RCT of group-CBT (O'Dowd, 2006) is included, then six out of eleven trials registered no overall effect. However, the Full Guideline states on page 198: "*Eight of the studies reported beneficial effects of CBT"*. This discrepancy may be explained as "positive spin" by the GDG, which distinguishes between some beneficial effect and no overall effect.

Such "positive spin" is also used about the Lloyd et al 1993 study (see below), which was given an overall positive rating for CBT when in fact the CBT effect was negative, but because in that study CBT was combined with immunoglobulin therapy (which had a positive effect), the RCT as a whole was given a positive outcome and is included in the five successful RCTs of CBT.

The five specific RCTs of CBT on which the GDG relied were:

1. Deale A, Chalder T, Marks I, Wessely S. Cognitive behaviour therapy for chronic fatigue syndrome: a randomised controlled trial. Am J Psychiat 1997:154:408-414 (60 patients)
2. Deale A, Husain K, Chalder T, Wessely S. Long-term outcome of cognitive behaviour therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow-up study. Am J Psychiat 2001:158:2038-2042 (this was a 5-year follow-up of their 1997 study and had 53 patients)
3. Lloyd AR, Hickie I, Brockman A, Hickie C, Wilson A, Dwyer J et al. Immunologic and psychiatric therapy for patients with chronic fatigue syndrome: a double-blind, placebo-controlled trial. Am J Med 1993:94:197-203 (90 patients). *Note that there is a discrepancy in the stated number of patients: page 54 in the 488 page Appendix (the York Review of 2005) gives the number of patients as 49, but this becomes 90 in the JRSM version of the same study*
4. Sharpe M, Hawton K, Simkin S, Surawy C, Hackmann A, Klimes I et al. Cognitive behaviour therapy for the chronic fatigue syndrome: a randomised controlled trial. BMJ 1996:312:22-26. (60 patients). *Note that there is an error given on page 54 in Appendix I in relation to this study: the date is written as 1998 but should be 1996*
5. Prins JB, Bleijenberg G, Bazelmans E, Elving DL, de Boo TM, Severens JL et al. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. Lancet 2001:357:841-847 (270 patients).

The correct number of patients in the Lloyd et al study is 90, not 49 as stated on page 54 in Appendix I (the York Systematic Review of October 2005).

Excluding the Deale et al follow-up study of the same patients, this gives a total of 480 patients out of an alleged UK total of 240,000 patients and is insufficient data upon which to recommend a national strategy.

The 2005 version of the York Review was modified and published again in the Journal of the Royal Society of Medicine in October 2006 (before the Guideline was published in August 2007). This version identified seven RCTs of CBT, which included two RCTs on children (Viner 2004 and Stulemeijer 2005) that were excluded from recommendation.

Those RCTs of CBT using the Oxford criteria (Deale at al 1997; Deale et al 2001 [i.e. the follow-up of the patients from the 1997 study]; Sharpe et al 1996) cannot be studying people with ME/CFS, since the pathognomonic feature of ME/CFS is post-exertional incapacitating fatigability combined with malaise, and this cardinal feature is excluded from the Oxford case definition. Despite this, NICE has relied on these studies to recommend CBT for patients with ME/CFS.

Of the remaining two RCTs, the Lloyd study used the Australian criteria, which have never been adopted internationally, and the Prins et al study used their own modification of the US CDC 1994 Fukuda et al

criteria (which themselves do not exclude patients with somatoform disorder: Ann Intern Med 1994:121:953-959 and the international medical literature increasingly expresses doubt about their usefulness, for example: Salit IE. J Rheumatol 1996:23:540-544; Jason et al. JCFS 1999:5:3-33; Jason et al. Evaluation and the Health Professions 2003:26:13-22; Darbishire L et al. BJGP 2003:53:491:441-445; Kennedy G et al. Ann Epidemiol 2004:14:95-100; Jason et al. JCFS 2004:12:1).

Although technically invalid because by definition it excluded those with ME/CFS, it is notable that there were many other methodological flaws in the Deale et al 1997 study. In this study of 60 patients, half received CBT in the form of *"graded activity and cognitive restructuring"* and half received "relaxation". The authors state: *"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 state 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 are cited as exclusion criteria; nine participants, however, are described as having 'major depression' and there were high levels of existing psychiatric morbidity in the study cohort. Outcome measures are 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 be 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 state: "*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 is mostly reported as averages, rather than giving actual numbers of patients. The authors acknowledge 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).

Although once again a technically invalid study in relation to ME/CFS (because it used the Oxford criteria, of which Sharpe was the leading author), the Sharpe et al study of 1996 merits comment. This again 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'. Surprisingly, (the study) has received a luke-warm response from a source one might expect to be more enthusiastic. (The ME Association) says of the Oxford study: 'The full weight of righteous zeal exhibited by the therapists does not seem to have produced anything more than a perfunctory change at the margins of the illness'. '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 Adviser 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, this 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.

The Prins et al study of 2001 which was included in the "best practice evidence-base" for the NICE Guideline's CBT management regime has received perhaps more legitimate criticism than any of the other three studies.

Prins et al state that out of 476 patients diagnosed with CFS, only 278 were eligible and willing to take part. Those who refused to take part, had they done so, may have altered the outcome substantially. Patients with pre-existing psychiatric comorbidity (one third of the subjects) were not excluded. From the outset, the authors excluded those with ME/CFS because they state that the fatigue they were studying was "*not the result of organic disease or ongoing exertion".* The authors acknowledge that there was a very high drop-out rate in the treatment arm, but do not provide reasons for the drop-outs, nor do they report if there were any adverse effects from the CBT. As noted by Martin Bland, Professor of Health Statistics at the University of York in a personal communication (6th June 2008), loss to follow-up of participants is a serious problem in this trial and the groups may no longer be comparable because in this trial, the drop-out is greater in the CBT group than in the control group. People who after randomisation refused CBT, or after starting CBT discontinued it were not followed up, but they should have been, for the control group contained people who, given the opportunity, would have refused to start or would have discontinued treatment, and it might plausibly be thought that such people would do less well than acceptors. Bland states: "*I think that this invalidates the entire Prins trial. There are methods which have been developed to impute missing data, but they do not appear to have been used".* If drop-outs were due to adverse effects, these should have been reported, since exclusion of these statistics would allow over-estimation of the alleged benefits of CBT. Further, people may drop out of a trial because – although not actively harmed by it -- they receive no benefit; this again was not included in the Prins study. Had they done so, it might have distorted their results in a manner that did not fit their required outcome, because the trial had *"cure of chronic fatigue syndrome as its explicit goal of therapy".*

Of major importance is the fact that Prins et al used their own modification of the 1994 CDC Fukuda et al case definition. Patients were eligible for the study if they met the CDC criteria with the exception of the requirement for four of eight additional symptoms (those symptoms being impaired memory or concentration; sore throat; tender cervical or axillary lymph nodes; muscle pain; multi-joint pain; new headaches; unrefreshing sleep, and post-exertional malaise). If these important symptoms are omitted from the entry criteria, one is left with idiopathic chronic fatigue, yet Prins et al refer to their study participants as having "CFS" according to the CDC 1994 criteria. This would seem to border on deceit. Nowhere is there any evidence that the patients fully recovered, and a key outcome did not support the authors' expectation, because for the CBT group: *"Differences in the time spent working in a job did not reach the 5% level of significance".* Despite this evidence, the authors still concluded: "*The results of this trial suggest that CBT can be transferred from CFS research clinics to therapists with no previous experience of CBT. To increase accessibility of this treatment for all CFS patients in future, CBT will have to be implemented outside university medical settings. This idea accords with Wessely and colleagues' suggestion of transferring the diagnosis and treatment of functional somatic syndromes to general physicians aided by psychiatrists. Ideally, general practitioners should diagnose CFS and refer patients to psychotherapists for CBT without detours to medical specialists, as in other functional somatic syndromes".*

The fact that NICE relied on this particular trial as the mainstay of its recommendations is disturbing.

Clearly NICE has ignored the cogent published criticisms of the Prins et al trial, for example: "*Judith Prins and colleagues' report leaves the clear impression that there is a powerful case for the provision of CBT as*

a specific therapy for CFS. However, careful assessment of published studies suggests that this impression is not evidence-based. Conclusions about efficacy must be tentative in view of the paucity of trials; the small number of patients involved; the difficulties in comparing CBT with control interventions and, importantly, the potential effect of publication bias" (Vance A Spence and Neil C Abbot. Lancet 2001:358:9277:239-240).

The Medical Director of the ME Association wrote to The Lancet pointing out: "*Although the purely psychosomatic explanation favoured by Prins and colleagues may well apply to one subgroup of patients with CFS, there are others in whom there is evidence of neurological, muscular and endocrine abnormalities which cannot be adequately explained by a psychosomatic model. Underlying organic pathology may help to explain (why) objective evidence of substantial and sustained recovery (ie. return to normal employment) is seldom achieved".*

A notable feature of these four studies is that they had different entry criteria and different (indeed, very diverse) outcome measurements, so cannot be compared. Indeed, the York Review (2005) acknowledged that: *"standardisation of outcomes are a priority for research".* All four studies were very small, and all have serious methodological flaws.

As noted by Abbot and Spence in 2006, the behavioural model of "CFS/ME" offers relatively little; it is supported only by researchers with a professional interest in psychosocial aspects of illness who have acquired the funding to test their hypotheses; the evidence-base for the usefulness of this model consists of a small number of clinical trials which, even by their own standards, have relatively unspectacular results, yet this model dominates the canvas (Lancet 2006:307:1574). This model certainly dominates the NICE management recommendations.

Based on these four studies (and one follow-up study), it is illogical for the GDG to recommend CBT as an effective intervention for all people with "CFS/ME" in the UK, especially as that term is said to include people with ME/CFS.

That the term "CFS/ME" is deemed by NICE to equate exactly to ME/CFS has been established by NICE:

"We were not able to find the CDC (US Centres for Disease Control) statement that the conditions were different?" (NICE CFS/ME Consultation Draft, 29th September – 24th November 2006, comments on Chapter 1; NICE CG53 website).

This is a remarkable statement by NICE, because the CDC website clearly confirms:

"***Various terms are incorrectly used interchangeably with CFS***. *The name ME was coined in the 1950s to clarify well-documented outbreaks of disease:* ***ME is accompanied by neurological and muscular signs and has a case definition distinct from that of CFS***". This is the CDC Continuing Education Course WB1032 (http://www.cdc.gov/cfs/cme/wb1032/chapter1/overview.html).

It is even more remarkable that in its comments on stakeholders' submissions, despite having had numerous submissions pointing out the need to subgroup "CFS" (including from The Royal College of Physicians of London and The British Psychological Society), the GDG asserted incorrectly seven times (for example, in their comments on the submission from The 25% ME Group for the Severely Affected (page 1 of 575); in their comments on submission from The ME Association (page 455-456 of 575); in their comments on the submission from The Young ME Sufferers Trust (page 490 of 575):

"*No research evidence was found for defined sub-groups or different management strategies".*

"While it is generally recognised that (CFS) is heterogeneous, the evidence does not allow distinctions between subgroups".

There is an abundance of evidence, but it is not contained in the four RCTs of CBT upon which the GDG chose to rely.

Professor Leonard Jason, without doubt one of the world's leading researchers into the disorder, has clarified this issue:

"The term ME/CFS is now being used in many countries, as proposed by the Canadian Case Definition (Carruthers et al, 2003).

"It is possible to distinguish between the two conditions, but if the current case definition of CFS does not identify patients with specific symptoms (e.g. post-exertional malaise), then it would be easy to miss some individuals who really have ME/CFS and to include others who do not have this illness. If this occurred, it would be impossible to identify consistent biological markers of this illness, and then many researchers and clinicians would conclude that ME/CFS was a psychosomatic illness.

*"**Clearly, some patients with this illness do have inflammation** and others do not (Exploratory subgrouping in CFS: Infectious, inflammatory, and other. Corradi, Jason & Torres-Harding, 2006. In: A Columbus (Ed): Advances in Psychology Research, Volume 41, pp 115-127; Hauppage, NY: Nova Science Publishers).*

"The current method of grouping all individuals who meet the CFS diagnostic criteria together is complicating the identification of biological markers that will help scientists to unravel the pathophysiology of this illness.

"The name myalgic encephalomyelitis has a 50 year history in the medical literature and it has been formally classified by the WHO as a neurological disease in the ICD since 1969 and remains classified in the current ICD as a neurological disorder (ICD-10 G93.3). In contrast, Myalgic Encephalopathy is not defined as a specific condition and has no ICD status. Many advocates believe that we would lose that 50 years of historical lineage if we endorsed the term Myalgic Encephalopathy.

"Many feel that there is considerable benefit of maintaining the name Myalgic Encephalomyelitis, which is the most consistently used and most widely recognised name worldwide, with an established neurological ICD code and a well-documented history of outbreaks along with extensive epidemiological investigations.

"Researchers and clinicians need to be aware of the strong sentiments that patients have for Myalgic Encephalomyelitis, which is historically correct (Ramsay 1981) and has been used internationally (Hyde, Goldstein & Levine, 1992)" (Issues Involved in Name Change Recommendations. Leonard A Jason et al. http://listserv.nodak.edu/cgi-bin/wa.exe?A2=ind0705B&L=CO-CURE&D=0&F=P&I=-3&P=3529&F).

Evidence about CBT for "CFS/ME" that did not inform the GDG's management recommendations

Other RCTs that were excluded from the GDG "evidence-base" have found no difference in outcome after CBT for patients with "CFS/ME", for example, Huibers and Beurskens et al's findings were unequivocal:

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

It is notable that this trial post-dates the Prins et al study, whose stated aim was to implement Wessely's intention of transferring the diagnosis and treatment of CFS to general practitioners, and that two of the authors were also co-authors of the Prins 2001 study (Bazelmans and Bleijenberg).

Work by Jason et al that casts significant doubt on the claimed efficacy of CBT was also ignored. Although his major review of non-pharmacologic interventions for CFS was published after the production of the Guideline (in this case, in December 2007, but members would have been expected to know about it; moreover, many of the references pre-date the Guideline so were available to the GDG), it is customary for authors of systematic reviews to seek, obtain and quote from articles in press. (For example, in their 2006

up-dated Review that was published in the JRSM, Chambers and Bagnall et al ought to have referred to the negative findings of the 2006 O'Dowd study of group-CBT, but they did not do so).

Jason et al are clear: "*Despite improvement found in a number of interventional studies* (referring to the Deale et al 1997 study and the Sharpe et al 1996 study upon which NICE relied)*, other studies have been less successful. Furthermore, physician-delivered CBT for CFS participants has not shown efficacy in two studies. In 2001, Ridsdale et al found that counselling was as effective as CBT.* ***Given the mixed results for these cognitive and behavioural interventions, it is unclear which type of non-pharmacologic intervention is most effective for participants with CFS****".* Jason et al make the point that even in their own trial of different forms and combinations of CBT, "*the changes in the present trial were relatively modest and few participants experienced remission of illness".* The authors also note the lack of long-term effects when the (very high) drop-put rates are taken into consideration.

In contrast to the Wessely School, Jason et al support a model of CBT which "*serves as a coping tool that allows the participant to view his/her reactions to the illness as understandable adjustments to an unpredictable, disabling condition"* and which *"might be considered an important management tool that can be* ***utilised as part of a comprehensive plan of medical and psychological treatment for patients with CFS"*** (J Clin Psychol Med Settings 2007:14:4:275-296).

In a personal communication, Jason wrote: "***I continue to believe that although some non-pharmacologic interventions can be helpful to some people in learning to better cope with many chronic conditions, from cancer to AIDS, they should not be used as the only treatment modality, and as we all know, this all too frequently occurs with ME/CFS"*** (25th July 2008).

A meta-analysis of CBT for CFS which does not accord with the NICE Guideline is that of Malouff et al from Australia; again this was published in 2007, but only 2 of 55 references post-date the Guideline (so 53 were available to the GDG). Malouff et al identified 13 studies that met their inclusion criteria and the authors were more stringent than the York reviewers upon whom the GDG relied, as Malouff et al excluded a study which Bagnall et al (the York reviewers) decided to include (in which a substantial number of participants received treatment after the study treatment -- Deale, Husain, Chalder and Wessely, 2001; reference 148 in the Guideline Appendix I). This is significant, because in the UK, it was stated on BBC Radio 4 (You and Yours; 7th November 2007) that Professor Trudie Chalder claimed that CBT is "*curative*" for 25% of patients, basing this assertion on her own study (Deale, Husain, Chalder and Wessely, 2001); NHS Plus claims that CBT will return people to gainful employment, based on the same 2001 study, and the NICE Guideline claims there is good evidence for the efficacy of CBT, again based on the same study (Deale et al 2001). However, as pointed out by Hooper & Reid, (http://www.meactionuk.org.uk/FINAL_on_NICE_for_Gibson.html), the data in that study was corrupted, so no reliable conclusions can be drawn from it. Malouff et al agreed, and declined to include it in their meta-analysis.

There is another interesting comparison: in their up-dated Review (2005) that was done specifically to support the work of NICE, Bagnall et al excluded a study by Ridsdale et al (Chronic fatigue in general practice: Is counselling as good as cognitive behaviour therapy? A UK randomised trial in primary care. British Journal of General Practice 2001:51:19-24) which found that counselling was just as effective as CBT, but Malouff et al included it as being essential for the comparative assessment of CBT. Bagnall et al had included this study in their JAMA 2001 Systematic Review yet, curiously, they excluded it from their 2005 Systematic Review of the same literature that was done to support the work of NICE. This would seem to be yet more evidence supporting the contention that the NICE Guideline was indeed a case of "policy-based evidence" and not "evidence-based policy".

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

Another significant study which does not support the NICE approach of combining all states of "medically unexplained fatigue" into a single somatoform disorder is that of Jason et al which provides clear evidence of how different subgroups of "CFS" may respond to nonpharmacologic interventions such as CBT (Baseline Cortisol Levels Predict Treatment Outcomes in Chronic Fatigue Syndrome Nonpharmacological Clinical Trial. JCFS 2007:14:4:39-59).

"*Early researchers describing nonpharmacologic behavioural interventions for CFS reported high levels of success (Deale, Chalder, Marks & Wessely, 1997, Prins et al 2001; Sharpe et al 1996), but more recent studies have had somewhat more mixed results (Bazelmans et al 2005; Donta et al 2003; Ridsdale et al 2004; Ridsdale et al 2001). Bazelmans et al found that those who improved the most had fewer complaints at baseline.*

"Cleare et al (2003) found that response was differentiated by baseline urinary cortisol levels, i.e. those with normal baseline levels responded more positively to the intervention than those with initial abnormally low levels.

"Those individuals with most impaired hypothalamic-pituitary-adrenal axis (HPA) function might be the least able to improve with nonpharamcologic interventions.

"It is possible that some individuals with CFS have a cortisol deficiency and others do not, but when all are combined into one large CFS category, these important differences are ignored.

*"**Understanding how nonpharmacologic interventions differentially affect the subgroups of individuals with CFS might provide insight into the pathophysiology of this illness".***

In this study, *"Among those with abnormal baseline cortisol, 63% had low activity levels at the 12-month follow-up, whereas among those with normal baseline cortisol, only 35% had low activity levels at the 12-month follow-up.*

*"**This indicates that those who are most impaired on HPA functioning might be least able to improve (with CBT)".***

Noting that immunologic functioning did not improve as a result of CBT (Peakman et al, 1997), this study also looked at disturbances of immune function, and found significant immunological abnormalities in the group with abnormal cortisol at baseline, suggesting that *"a stimulus, present in these individuals but absent in the normal cortisol group, is responsible. (This) likely represents an important component of the immune dysfunction associated with the pathogenetic process of CFS.*

*"**In summary, subgroups of individuals with either normal or abnormal cortisol levels exhibited different outcomes in a nonpharmacologic treatment trial.***

"This suggests that cortisol levels may serve as an important marker for individuals with CFS that might benefit from CBT.

***"This study suggests that subgrouping according to endocrinologic functioning is a useful strategy for assessing the effects of treatment**".*

It is the case that the NICE Guideline proscribes testing cortisol levels and regards all cases of "CFS/ME" as a behavioural disorder.

By strategically limiting its selected "evidence-base" to just four RCTs of CBT, the GDG has ignored a wealth of good quality studies and empirical evidence which question the reliability of those RCTs.

Wessely School psychiatrists often accuse patients with ME/CFS of "catastrophising" their symptoms, and of holding "catastrophic illness beliefs", but the chosen RCTs do not address symptoms of ME/CFS other

than "fatigue", 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). Wessely School psychiatrists exclude such patients from their studies. Consequently, the NICE Guideline does not accord such symptoms sufficient prominence.

In summary, there is no credible evidence to support the GDG's claim that the evidence-base for "best practice" is the nationwide implementation of CBT/GET for patients with "CFS/ME" if, as stated, this includes patients with ME/CFS.

Even the authors of the first York Systematic Review (2001) themselves offered many cautions about their results (including poor quality evidence; the studies were methodologically flawed; inconsistencies in case definitions; exclusion of the severely affected and children etc) but these caveats were largely missing from the 2005 version that was compiled by the same authors specifically to support the work of NICE.

Missing evidence for the NICE recommendations

It is notable that the RCTs upon which the GDG relied all promote the Wessely School model of CBT (i.e. the need to change aberrant illness beliefs about the nature of the disorder by the re-structuring of cognitions, increase of physical activity, and the return to work). This required patients to push themselves beyond their physical capabilities and was based on the "no pain, no gain" philosophy (eg. Fulcher and White, BMJ 1997:314:1647-1652, which stipulated: *"If patients complained of increased fatigue they were instructed to continue at the same level of exercise and increase when the fatigue had lessened. All patients were instructed to continue with regular exercise"*). A disturbing number of patients have reported in numerous ME/CFS support group magazines that they were subjected to rigorous, oppressive and even abusive regimes. In one shocking case, the mother of a child severely affected by ME/CFS discovered that the therapist had written a treatment plan and that this plan stated *"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*" (http://wwwmeactionuk.org.uk/Inquest_Implications.htm).

However, the actual advice in the NICE Guideline has modified somewhat this disproved model and is more focused on psychological support and helpful coping strategies that are to be undertaken with the co-operation of the patient (i.e. working in partnership with the patient). This is very different from the original Wessely School model.

Whilst this is to be welcomed, it nevertheless presents another problem for NICE. There are no RCTs for this modified version of CBT, so on what best practice evidence-base does NICE rely for its national policy recommendations?

None is provided.

The Cochrane Collaboration Review of CBT for "CFS/ME"

It is likely that in its defence of the Guideline, NICE will rely on the latest revision of the Cochrane Collaboration (CC) Intervention Review of CBT for CFS ("Cognitive behaviour therapy for chronic fatigue syndrome in adults". Jonathan Price et al. Cochrane Database of Systematic Reviews, vol 16 #3, July 2008. John Wiley & Sons).

As customary with this body, this Review comes under the Cochrane Depression, Anxiety and Neurosis Editorial Group, which means that the WHO-classified CFS is incorrectly categorised by the CC as a mental disorder, which is in breach of the WHO taxonomic principles. However, the CC Review clearly states: "*CFS has had many names in recent decades, including myalgic encephalomyelitis (ME) and post-*

viral fatigue syndrome" but, according to the WHO rubric, the inclusion of ME/CFS as a mental disorder is indefensible.

The CC reviewers claim that "CFS" has been *"clearly defined",* yet they have failed to consider the evidence that people with ME/CFS do not suffer from "fatigue" but from post-exertional fatigability. This pathognomonic feature does not feature at all in the Wessely School model, which may mean that the studies in the CC Review have excluded people with ME/CFS.

The process of reviewing the literature for CBT in CFS began in 1997, and in the original CC 2000 Review, no meta-analyses were performed, since only three studies were eligible for inclusion at that time, and each of those studies used a different control intervention. The conclusions of the original Review stated: "*There is no satisfactory evidence for the effectiveness of CBT in patients with the milder form of CFS found in primary care or in patients who are so disabled that they are unable to attend out-patients. Additionally, there is no satisfactory evidence for the effectiveness of group CBT".*

This latest CC up-date of CBT for CFS includes an additional 12 studies conducted since 1999.

The selection criteria were RCTs involving adults with a primary diagnosis of CFS assigned to a CBT group compared with usual medical care (this is not defined) or another intervention, alone or in combination.

15 studies (1043 participants) were included in the Review, of which 4 studies (i.e. more than 25%) are unpublished (and therefore not peer-reviewed).

The four RCTs of CBT that formed the basis of the GDG's management recommendations are all included in the up-dated Cochrane Review (Deale et al, Am J Psychiat 1997; Lloyd et al, Am J Med 1993; Sharpe et al, BMJ 1996 and Prins et al, Lancet 2001).

The up-dated Cochrane Review found that 40% of people who received CBT showed clinical improvement, in contrast with 26% who received usual medical care.

The recommendation is that more studies should be carried out.

However, the CC Review in fact concluded that the results were inconsistent and the studies did not fit well together, making it difficult to draw any conclusions.

At follow-up (1 – 7 months after treatment ended), when people who had dropped out were included, there was no difference between CBT and usual medical care. Very few studies reported on the acceptability of CBT and no studies examined side-effects.

The Cochrane Collaboration is deemed by the Establishment to be the "gold-standard" of meta-analyses. Cochrane Reviews are generally assumed to be independent and objective, but there are known problems with them (Ole Olsen, Andrew Herxheimer et al; BMJ 2001:323:829-832).

Olsen et al noted that whilst the Cochrane Library *"remains a key source of evidence about the effects of healthcare interventions, its users should interpret reviews cautiously. Readers should be particularly cautious of reviews with conclusions that favour experimental interventions when relatively little evidence is available for the review. Too often, reviewers' conclusions over-rated the benefits of new interventions".*

Given this warning, it may be deduced that, despite its own conclusions that at follow-up there is no difference between CBT and usual medical care, the CC's latest call for even more studies of CBT on long-suffering ME/CFS patients shows an illogical resistance to accept the existing evidence that it is ineffective unless subgrouping is carefully utilised (which NICE does not accept).

Conclusion

There is a basic question that is never addressed by those who favour the psychosocial model of "CFS/ME": if patients are not cured by psychotherapy (a fact which the Wessely School themselves concede: CBT and GET are only *"modestly effective"* and *"neither approach is remotely curative"* – Simon Wessely, Editorial, JAMA 19th September 2001), then what is it that they are not cured from?

If, as the Wessely School has advised NICE, "CFS/ME" is a psychological disorder, then if a psychological therapy has not cured it, this means either that it is not a psychological disorder, or else that the psychological therapy does not work.

Why, then, does the NICE Guideline recommend only a psychological therapy for "CFS/ME" (which is said to include ME/CFS) that has been clearly shown not to be effective?

Patients would not complain so vociferously and consistently about a management regime that helped them, whether that regime be orthodox, alternative, psychological or of any other type, but with CBT and GET, patients have registered their complaints and concerns for many years, as has been demonstrated in the many surveys conducted by the UK ME charities. The only possible conclusion must be that these approaches do not work and / or are harmful.

The Guideline Development Group which produced the Guideline, however, deemed the patients' evidence to be biased and it was therefore largely disregarded:

"Information gathered through patients surveys is generally considered as relatively low-level evidence. RCTs are considered to be at the top of the hierarchy of evidence (and) when evidence from an RCT is available, it is generally given priority over other types of evidence, including patient surveys. The GDG recognised that surveys from self-selected respondents are subject to bias" (Full Guideline, 2.6.1, pp 77-78).

This was confirmed by Dr Fred Nye, a member of the GDG:

"*All statements which the GDG had rated as 'uncertain' were submitted to a wider group, of whom the majority were patients and carers, and was much more confident in its views than the GDG. This suggests very strongly that its conclusions were based on opinion rather than on a serious review of the evidence. Consultation with the wider group was more like an opinion poll. In my view it did little to increase the objectivity of our recommendations"* (J Inf. 2007:55:6:569-571).

This would seem to be a gross procedural abnormality, because not to accord patients' evidence equal weighting with RCTs is in clear breach of the AGREE Instrument. That NICE is a member of the AGREE collaboration was confirmed by Professor Sir Michael Rawlins, Chairman of NICE, on 18th April 2002: "*The Scottish Intercollegiate Guidelines Network (SIGN) and NICE are both members of the AGREE (Appraisal of Guidelines, Research and Evaluation) collaboration. Members of the AGREE collaboration all develop guidelines according to the same basic principles and both NICE and SIGN aim to meet the international standard set by the AGREE guideline appraisal instrument (available from www.agreecollaboration.org)"* (Joint NICE / SIGN statement on working together to improve patient care, 18th April 2002).

In the case of its Guideline on "CFS/ME", NICE has done little to improve patient care.