

**EVIDENCE THAT THE GUIDELINE DEVELOPMENT GROUP THAT PRODUCED THE NICE  
GUIDELINE ON CFS/ME (CG53) FAILED TO FULFIL ITS REMIT**  
**(particularly in relation to the potential dangers of graded exercise therapy)**

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**Executive Summary**

It is a matter of record that Myalgic Encephalomyelitis (ME) has been listed by the World Health Organisation (WHO) as a neurological disorder since 1969. ME was officially recognised in the UK as a nosological entity by the Royal Society of Medicine in 1978, and in November 1987 ME was officially recognised by the Department of Health, who accepted it as an organic disorder. 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. “ME/CFS” is not the same as “CFS/ME”, which refers to undifferentiated states of “chronic fatigue”.

It might be presumed, therefore, that those suffering from ME/CFS would receive the help and support that they need as a matter of course, as would be expected by anyone suffering from a serious, chronic, neurological disorder. However, for the vast majority of ME/CFS sufferers in the UK this is not the case, with the first-line (indeed only) interventions recommended by NICE being two behavioural interventions (Cognitive Behavioural Therapy [CBT] and Graded Exercise Therapy [GET] ) that are designed to convince sufferers that they are not physically sick - hence the pressing need for a Judicial Review of the NICE Guideline CG53 on “CFS/ME” (as the illness is referred to in the Guideline) produced in August 2007, a Guideline that could potentially adversely affect the lives of tens of thousands of seriously ill people.

This document looks specifically at three key areas of concern in relation to that Guideline, in which it is submitted that the Guideline Development Group (GDG) that had the task of producing the Guideline failed to fulfil its remit in those three areas, a failure that underpins the plight and lack of understanding and support shown to those with ME/CFS in the UK.

Those three areas are as follows -

**(i) Assessment and Diagnosis**

- The GDG did not clarify the confusion surrounding terminology and therefore failed in its remit to produce a Guideline to aid diagnosis, considering instead a wide ranging spectrum of fatigue states
- The case definition created by the GDG cannot differentiate those with ME/CFS from anyone with unexplained chronic fatigue, because it excludes so much of the well-documented symptomatology of ME/CFS whilst emphasising key features of a behavioural disorder
- NICE itself acknowledges the WHO classification of ME/CFS, yet there is disparity between NICE and the GDG: the consensus of the GDG members does not accept the neurological status of ME/CFS, thereby failing to identify or define the specific disorder ME/CFS to which the Guideline purports to relate
- Members of the GDG failed to acquaint themselves fully with the existing knowledge base about ME/CFS by stating that consideration of the aetiology was not in their remit - yet that existing knowledge base includes over 4,000 published studies showing underlying biological abnormalities in ME/CFS patients.

**(ii) Symptom Management**

- The GDG was selective in its acceptance of the documented signs and symptoms seen in ME/CFS
- The NICE Guideline states that there are no abnormal signs in “CFS/ME”. This conflicts with international research showing many well-documented abnormal signs in ME/CFS

- The documented symptoms of ME/CFS bear little resemblance to “chronic fatigue” or to a “continuum of on-going tiredness”, a description of “CFS/ME” often used by those who believe it to be a behavioural disorder
- By excluding from consideration the existing evidence-base on ME/CFS, the GDG failed to acknowledge the existence of many signs and symptoms of ME/CFS, with the result that the Guideline fails to offer correct advice to GPs about symptom recognition and management.

### (iii) Rehabilitation Strategies

- The GDG confined its management recommendations to behavioural modification techniques
- The recommended graded exercise plan in the Guideline specifies that the intensity of GET should be incrementally increased, leading to aerobic exercise. This is in direct contradiction to the advice of well-known international experts on ME/CFS
- The GDG dismissed submitted evidence that people with mild to moderate ME/CFS have been made worse by GET and have become severely affected
- Concerns about the Randomised Controlled Trials (RCTs) that bear no relationship to the specific disorder ME/CFS and upon which the GDG placed undue reliance were well known before the publication of the Guideline - and although pointed out to the GDG, these concerns were ignored
- No consideration was given to the international concerns about GET, and contra-indications to the use of GET in ME/CFS were ignored
- The GDG ignored elements of the Chief Medical Officer’s Working Group Report on “CFS/ME” of January 2002, a Report that recorded concern about GET
- Surveys of almost 5,000 patients carried out by UK ME/CFS charities have shown unequivocally that GET is unacceptable and can be actively harmful to patients with ME/CFS
- GET and CBT are already known not to be effective, and this is acknowledged by the proponents of GET and CBT themselves
- Numerous interventions used by international experts which many ME/CFS sufferers have found to be helpful are proscribed by the GDG on the basis that there are no RCTs, for example, thyroid and adrenal support, anti-viral drugs, dietary changes (patients’ evidence was dismissed by the GDG when it should have been accorded equal weighting with RCTs).

### Conclusion

- The GDG has failed in all three aspects of its remit; the Guideline should therefore be withdrawn
- A new Guideline is required, prepared by a different, more balanced and representative GDG
- A new GDG should be required to consider the totality of the existing evidence-base on ME/CFS and to heed the many calls for a recommendation that the direction of future research should focus on the biomedical aspects of the disorder and thus towards a diagnostic test (thereby separating ME/CFS from “chronic fatigue”)
- A new GDG should be required to be mindful of the pressing need for appropriate (as distinct from basic) laboratory and neuro-imaging investigations as occurs in other countries
- The general body of knowledge concerning ME/CFS that is known about by clinicians and researchers working in the field is now so great that it should be considered serious professional misconduct to pretend that it does not exist, or to ignore it as the GDG did
- The GDG members were specifically directed (i) not to consider the existing evidence-base on ME/CFS, thereby intentionally obfuscating the distinction between psychiatric somatic disorders such as neurasthenia and neurobiological / autoimmune disorders such as ME/CFS (ii) not to place the disorder in any nosological context and (iii) to adopt an inclusive approach and wide-ranging definition of “fatigue”; the resultant Guideline therefore seems to be a clear example of the deliberate construction of “policy-based evidence” and not “evidence-based policy”.

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**Official Status of a NICE Guideline**

As long ago as 1994 (i.e. before the foundation of NICE in 1999), a leading medical defence union warned its members that: *“If guidelines have been produced from a respected body and they have been accepted by a large part of the medical profession, a doctor will have to have strong reasons for not following the guidance”*.

Since the inception of NICE in 1999, the Commission for Health Improvement (which worked in collusion with NICE but which ceased existence in 2004 and became The Healthcare Commission – an “independent” watchdog for healthcare, now The Commission for Healthcare Audit and Inspection) has powers to monitor such guidelines and to ensure that they are implemented and observed.

Professor Sir Michael Rawlins, Chairman of NICE since its inception, is reported to have said: *“NICE guidelines are likely to constitute a reasonable body of opinion for the purposes of litigation. Doctors are advised to record their reasons for deviating from guidelines. A deviation may not be regarded as logically defensible. Healthcare professionals who adhere to guidelines with the authoritative stamp of bodies such as NICE are unlikely to be found guilty of negligence”* (Clinical practice guidelines and the law. Dr Peter Ellis. <http://www.lambchambers.co.uk/docs/art6.pdf> ).

There is a difference between a Guideline and a Health Technology Appraisal. Technology appraisals of medicines are mandatory. Clinical Guidelines advise on appropriate treatment and care of patients with specific conditions. Their implementation is not mandatory (House of Commons Publications and Records Select Committee on Health / NICE / January 2007).

However, some Primary Care Trusts state that a Guideline is indeed mandatory and must be complied with (<http://www.rotherhamhospital.trent.nhs.uk/BOGDocuments/MinsBoG13.06.07.pdf> ).

The NHS is required to provide a NICE-recommended treatment three months after the production of a Guideline.

Given the weight of authority accorded to NICE Guidelines, it is clearly imperative for the NICE Guidelines to be correct in all respects.

Unfortunately, in the case of its Guideline 53 on “CFS/ME”, in key areas NICE did not get its Guideline right.

**NICE’s remit on Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME)**

The Guideline CG53 on “CFS/ME” was issued on 22<sup>nd</sup> August 2007.

The remit of the NICE Guideline Development Group (GDG) was to produce a Guideline on (i) **assessment and diagnosis** (ii) **symptom management** and (iii) **rehabilitation strategies** for adults and children with CFS/ME. The remit specifically stated: *“As the management of CFS/ME depends on a correct diagnosis, the guideline will include recommendations about the process of assessment leading to a diagnosis. This will include (the) clinical case definition”* (Remit Scope:4.3[b]).

In defiance of the many informed submissions of concern, the final Guideline failed on all three counts.

The remit came from the Department of Health (DoH). The lead adviser on “CFS/ME” to the DoH is Professor Anthony Pinching, who was Chairman of the Investment Steering Group that devised the process and the criteria for setting up the Government’s 13 “CFS” Centres (see below); he oversaw the assessment of bids and he allocated the funds. He is one of the 13 Clinical Champions, heading the CFS Centre for the South-West of England; he is Associate Dean of the Peninsula Medical School and is Principal Medical Adviser to the charity Action for ME (Co-Cure ACT:13<sup>th</sup> February 2005).

Pinching’s views about the disorder are well-known. During the time he was Deputy Chair of the Chief Medical Officer’s Working Group Report on “CFS/ME” that was published in January 2002, Pinching stated his views in an article in Prescribers’ Journal that was published by the DoH. In that article, he said:

- *“The clinical features (of CFS) are unexplained fatigue lasting for over six months, **not related to ongoing exertion**”*
- *“The Oxford criteria (see below) are too narrow for clinical use”*
- *“Over-investigation can be harmful to the management of these patients, causing them to seek abnormal test results to validate their illness ”*
- *“It is helpful to establish with the patient a way of thinking about the illness ”*
- *“The benefits of graded exercise have been shown by randomised controlled trials ”*
- *“A behavioural response is crucial ”*
- *“Complementary therapists may reinforce unhelpful illness beliefs ”*
- *“**The essence of treatment is activity management and graded rehabilitation** ”*

(“Chronic Fatigue Syndrome”: Anthony J Pinching. Prescribers’ Journal: 2000:40:2:99-106).

During his tenure as Deputy Chairman of the CMO’s Working Group, Pinching opposed the call for sub-grouping of the heterogeneous term “CFS”; his views are set out in the final Report: the question of subgroups “*may be considered a matter of semantics and personal philosophy*” (Annex 3, section 3). This does not accord with the views of international experts (see below).

Professor Pinching was one of the advisers on the choice of GDG membership. It is the case that clinicians and scientists experienced in ME/CFS who offered their services and who wished to be included on the GDG were refused and received letters of rejection.

Re: Diagnosis:

- The GDG failed to identify or define the disorder to which the Guideline purported to relate, considering instead a wide ranging spectrum of fatigue states (but still referring to these as “CFS/ME”)
- The GDG failed to accept both the national and international classification of the disorder and thus the correct status of the disorder
- The GDG failed to consider the existing evidence-base about the disorder under review.

Re: Symptom Management:

- The GDG ignored and thus excluded from consideration cardinal symptomatology of the disorder that has been observed and documented by experienced clinicians for the last 70 years and therefore failed to provide appropriate guidance on symptom management.

Re: Rehabilitation Strategies:

- The GDG confined its management recommendations to behavioural modification techniques that are based on the assumption that improvement and even cure is possible if the patients’ aberrant illness beliefs are corrected by psychotherapy. In this respect, the GDG placed undue reliance on a small number of flawed studies that bear no relationship to the specific disorder ME/CFS.

### **Failure to offer guidance on diagnosis**

#### 1. Failure to identify or define the disorder to which the Guideline purports to relate

The GDG did not use the opportunity to clarify the confusion surrounding terminology and therefore failed in its remit to produce an aid to diagnosis.

ME has been documented in the medical literature since 1934 (Gilliam AG. Public Health Bulletin, US Treasury Department No.240: 1938). In 1962, the distinguished neurologist Lord Brain included it in the standard textbook of neurology (Diseases of the Nervous System. Lord Brain. Sixth Edition. Oxford University Press 1962). ME was formally classified by the World Health Organisation (WHO) in the International Classification of Diseases as a neurological disorder in 1969 (ICD-8: Vol I: code 323, page 158; Vol II: Code Index, page 173). On 7<sup>th</sup> April 1978 the Royal Society of Medicine held a symposium on ME at which it was accepted as a distinct nosological entity (Post Grad Med J 1978;54:637:705-774).

Because the WHO International Classification of Diseases (ICD-10, issued in 1992) uses the term “CFS” as one by which ME may be known, the US International Association for CFS formally adopted the term “ME/CFS”: this term refers to a specific nosological entity. This distinct disease is classified in the current ICD-10 at G93.3 under Diseases of the Nervous System.

ME/CFS is not the same – and does not mean the same -- as the term “CFS/ME” used by NICE. That term was introduced by certain UK psychiatrists who claim that ME does not exist except in the minds of those who think they suffer from it. These psychiatrists (who are advisers to Government bodies including the Department for Work and Pensions and are influential at State agencies such as the Medical Research Council and NICE, and who are advisers to the Centre for Reviews and Dissemination at York) reject 70 years of published clinical and scientific evidence and assert that “CFS/ME” is a behavioural disorder. This term (“CFS/ME”) was coined by these psychiatrists and was used in the Chief Medical Officer’s Working Group Report on CFS of January 2002 to which they were advisers. The source of the term was explained thus: *“It may seem that adopting the lay label (of ME) reinforces the perceived disability. A compromise strategy is ‘constructive labelling’: it would mean treating chronic fatigue syndrome as a legitimate illness while gradually expanding understanding of the condition to incorporate the psychological and social dimensions. The recent adoption by the UK Medical Research Council and the Chief Medical Officer’s report of the term CFS/ME reflects such a compromise”* (B Fischhoff, Simon Wessely. BMJ 2003;326:595-597).

The CMO’s Working Group Report of 2002 failed to acknowledge that ME/CFS is a formally-classified neurological disorder and instead stated: *“CFS/ME is clearly not a single diagnostic entity, but a symptom complex in which dysfunction is multifactorial in origin”* and further stated: *“many fatiguing syndromes overlap, and to define boundaries is difficult, and to some extent artificial. This overlapping makes incidence and prevalence studies difficult, and means that the findings are very prone to variation due to differences in case definitions used”* (Annex 1, not published in hardback but only on-line). A small but influential group of UK psychiatrists and mental health workers (colloquially known as the “Wessely School (Hansard [Lords] 19<sup>th</sup> December 1998:1013), whose most prolific author is Professor Simon Wessely from Guys, Kings and St Thomas’ School of Medicine and The Institute of Psychiatry, London, and who maintain that “CFS/ME” is a behavioural disorder, was heavily represented in the Working Group.

On 22<sup>nd</sup> January 2004, Andre L’Hours from the WHO headquarters in Geneva confirmed in writing that: ***“According to the taxonomic principles governing ICD-10 it is not permitted for the same condition to be classified to more than one rubric as this would mean that the individual categories and subcategories were no longer mutually exclusive”***.

This clearly means that ME/CFS cannot be subsumed into any category other than G93.3 (neurological) and it cannot be considered the same disorder as “unexplained chronic fatigue” or neurasthenia, which are classified under behavioural disorders at F48.0. This is important, because Professor Wessely has long argued that *“Neurasthenia would readily suffice for ME”* (Lancet 1993;342:1247-1248) and was instrumental in a Cochrane Review that says: *“There are suggestions that chronic fatigue syndrome*

(sometimes called *myalgic encephalomyelitis*) may be identical to *neurasthenia*” (Cochrane Collaboration Depression, Anxiety & Neurosis Group Review Group [CCDAN], which includes Professor Wessely and which was officially registered in June 1996). This document unequivocally categorises CFS as a mental health disorder: **“The CCDAN is concerned with the evaluation of healthcare relevant to mood disorders, somatoform disorders, chronic fatigue syndrome, eating disorders and deliberate self-harm”** (<http://www.mrw.interscience.wiley.com/cochrane/clabout/articles/DEPRESSN/frame.html> ).

The US Centres for Disease Control (CDC) website confirms that: *“The name ME was coined in the 1950s to clarify well-documented outbreaks of disease; ME is accompanied by neurological and muscular signs (sic) and has a case definition distinct from that of CFS(ME)”*. (<http://www.cdc.gov/cfs/cme/wb1032/chapter1/overview.html> ).

The cardinal and defining feature of ME is exercise intolerance. People with ME cannot improve with exercise. Dr Melvin Ramsay, who in the UK was known as the “Father of ME” from his 30 year involvement with the disorder and who wrote some of the most accurate clinical descriptions of the disease, maintained that without exercise intolerance, a diagnosis of ME should not be made (<http://www.meactionuk.org.uk/ramsey.html> ).

Dr Elizabeth Dowsett, a former President of the ME Association, explains: *“There is ample evidence that ME is primarily a neurological illness, although non-neurological complications affecting the liver, cardiac and skeletal muscle, endocrine and lymphoid tissues are also recognised. The commonest causes of relapse are physical or mental over-exertion. The prescription of increasing exercise can only be counter-productive. **Some 20% have progressive and frequently undiagnosed degeneration of cardiac muscle which has led, in several cases, to sudden death following exercise.** Neurological problems include **exhaustion, weakness and collapse following mental or physical exertion beyond the patient’s capacity.** This arises from metabolic damage. **Problems with balance are common in ME due to involvement of spinal nerve tracts in the damaged brain stem.** Over 70% of ME patients suffer from significant bone and muscle pain (a further consequence of brain stem damage which seriously affects their mobility). Other patients have in addition metabolic damage to muscle fibres. 30% of patients with abnormal exercise tests have evidence of persistent infection in the muscles, and evidence of muscle infarcts. (Patients with ME exhibit) jitter due to incoordinated muscle fibre action, following damage to the neuromuscular junction. Patients with ME suffer a variety of symptoms arising from autonomic nervous system dysfunction, including liability to a dangerous drop in blood pressure on standing for more than a few minutes”* (<http://www.25megroup.org/Information/Medical/dowsett's/mobility%20problems.htm> ).

Since 1938, there have been thousands of published papers in the medical literature that document biological abnormalities in ME/CFS and there are also many books, both self-help and medical textbooks, some of the best being (1) *Postviral Fatigue Syndrome*; A Melvin Ramsay; published by Gower Medical Publishing, London, 1986; reprinted as *Myalgic Encephalomyelitis and Postviral Fatigue States*; Gower Medical Publishing, London, 1988 (2) *Myalgic Encephalomyelitis*; Celia Wookey; published by Croom Helm Ltd 1986; reprinted 1988 and 1989, Chapman and Hall Ltd – essential reading, as this book provides numerous case histories that cannot be bettered as teaching material; (3) *Post-Viral Fatigue Syndrome*; edited by Rachel Jenkins and James Mowbray; published by John Wiley & Sons, Chichester 1991; (4) *The Disease of a Thousand Names: Chronic Fatigue / Immune Dysfunction Syndrome*; David S Bell; published by Pollard Publications, Lyndonville, New York 1991; (5) *The Clinical and Scientific Basis of Myalgic Encephalomyelitis Chronic Fatigue Syndrome*; edited by Byron M Hyde, Jay Goldstein and Paul Levine, published by The Nightingale Research Foundation, Ottawa, 1992; (6) *Chronic Fatigue Syndrome and the Body’s Immune Defense System*; Roberto Patarca-Montero; published by Haworth Medical Press, 2002; and (7) *Chronic Fatigue Syndrome – A Biological Approach*; edited by Patrick Englebienne and Kenny De Meirleir; published by CRC Press, 2002.

No-one who is aware of this wealth of information can credibly doubt the reality, the validity and the devastation of this organic multi-system disease.

By its use of the contrived term “CFS/ME”, the NICE Guideline cannot be talking about the specific disorder ME/CFS, but about a heterogeneous group of people who suffer chronic fatigue arising from a variety of causes.

This is clearly so, because the Full Guideline states: *“It is unclear whether CFS/ME is one condition or part of a spectrum of similar conditions that have overlapping features”* (Section 5.4, page 186). The draft Guideline was even more dogmatic: *“A view held by a few individuals on the GDG was that CFS/ME could not be identified or managed unless a broader view was taken”* (Section 5.5, page 133). One of the patient representatives on the GDG (Tanya Harrison) challenged the fact that if only “a few” members of the GDG held that view, why was their opinion allowed to dominate the recommended management regime?

Despite the re-wording, it is still the case that the opinion and beliefs of GDG members who subscribe to the “broader view” have dominated the management and rehabilitation recommendations.

Although it is claimed by some that a “link” was made between ME/CFS and “chronic fatigue” in 2000, this does not accord with the substantial body of published evidence that ME/CFS is not the same as “chronic fatigue” – the American Medical Association confirmed as long ago as 1990 that the two are not the same: *“A news release in the July 4 packet confused chronic fatigue with chronic fatigue syndrome; the two are not the same. We regret the error and any confusion it may have caused”*.

Of concern is the fact that such amalgamation by the GDG has had a significant impact upon the blanket management regime recommended for “CFS/ME” (see below).

As the ScotME Group stated in their submission of January 2006 to the Gibson Inquiry held at the Palace of Westminster, the adoption of broad “fatigue” definitions has contributed to a fundamental misunderstanding about the nature of ME/CFS. Referring to those who conflate “chronic fatigue” with “chronic fatigue syndrome”, one US physician with over a decade of experience of ME/CFS observed: *“They often fail to distinguish between ‘chronic fatigue’ and ‘chronic fatigue syndrome’. The former is a fairly common symptom in medical clinics that does have a high linkage to already-present psychological problems. The latter is a specific medical condition. Their sloppiness has led to all kinds of trouble and misunderstandings”* (<http://www.immunesupport.com> 23<sup>rd</sup> January 2003).

As noted by Professor Malcolm Hooper before the NICE Guideline was published: *“An ill-founded approach offers a common psychiatric explanation for these syndromes (of uncertain origin). The disputed claims of some psychiatrists that all these syndromes are expressions of somatisation or are exemplified by the biopsychosocial theory lack an intellectually sound basis. The introduction of the word ‘fatigue’ has provided ample scope for error and confusion. Today, many patients with fatigue as a major feature of their illness are being diagnosed with CFS. There can be little doubt now that ME is correctly described as an encephalitis with up-regulation of pro-inflammatory immune responses, coupled with down-regulation of suppressor cytokines. This, coupled with the association of NTE (neuropathy target esterase) genes, validates the WHO nomenclature and classification under neurology. Undoubtedly, the perverse use of CFS to impose a psychiatric definition for ME/CFS by associating it with fatigue syndromes has delayed research, the discovery of effective treatment(s) and care and support for those with (ME/CFS)”* (J Clin Pathol 2007;60:466-471).

It is notable that shortly after the High Court (Cranston J) granted permission on 17<sup>th</sup> June 2008 to proceed to a full Judicial Review of the NICE Guideline, for which Hooper is an expert witness, something curious happened about his paper in the Journal of Clinical Pathology: although the paper had been published for over a year (since May 2007, having been peer-reviewed and having satisfied the BMJ Publishing Group lawyers), it was announced on the internet that Hooper had retracted his paper. Professor Hooper was not contacted by the JCP and initially knew nothing about the alleged retraction. Immoderate comment abounded on the internet that it had been retracted because it was flawed. The JCP’s website did indeed carry a notice that the paper had been retracted. Retraction of a published paper is a serious matter because it confers disgrace on the author(s) and is damaging, having global implications on the author’s credibility and reputation. Following investigations and negotiations with the Queen’s solicitors, Farrer & Co, who also act for the BMJ Publishing Group, the following statement was agreed: *“The BMJ Group wishes to*

inform readers that a series of technical errors resulted in the unjustified retraction of the article 'Myalgic Encephalomyelitis: a review with emphasis on key findings in biomedical research'. The article's citation remains as originally published (*J Clin Pathol* 2007;60:466-471; doi10.1136/jcp.2006.042408). The *Journal of Clinical Pathology* offers an unreserved apology to the author of the article, Professor Malcolm Hooper, and regrets any confusion or distress that may have been caused". This was to be referred to on the home page of the website (<http://jcp.bmj.com>) by saying "A statement from the BMJ Group – Myalgic Encephalomyelitis: a review by Malcolm Hooper" and the statement was also to appear in a hard copy of the Journal.

This was acknowledged by the JCP to be a very serious and unfortunate incident.

During the preparation of the Guideline, Dr Derek Pheby, Project Co-ordinator at The National ME Observatory, pointed out to NICE that: "***The diagnostic criteria detailed in paragraph 1.2.1.2 do not conform to any existing clinical case definition for CFS/ME***".

The case definition created by the GDG has not been validated or operationalised, so its predictive ability is unknown. One thing is certain: it cannot, by definition, differentiate those with ME/CFS from anyone with unexplained chronic fatigue, because it excludes so much of the well-documented symptomatology of ME/CFS whilst specifically including key features of a behavioural disorder. For example, it emphasises "unhelpful beliefs"; "the relationship between thoughts, feelings, behaviours and symptoms", and it emphasises that the management strategy will include "identifying perpetuating factors that may maintain CFS/ME symptoms" and that it will address "any over-vigilance to symptoms", stressing "predisposing, precipitating and perpetuating factors in CFS/ME" as a key area upon which future research should be focused. This reflects the assumption that CFS/ME is a "faulty belief system" that can be "corrected" by CBT and incremental aerobic exercise. **The reality is that more than one UK Coroner (and many more internationally) has accepted ME/CFS as a cause of death.**

The GDG's advice about the direction of future research is at odds with that of international experts, who for over a decade have been urging the need for research that would deliver a diagnostic test for ME/CFS. Correct diagnosis is crucial. In one area of the UK (Newcastle), the North of Tyne medical team screens patients referred with "CFS/ME" and over the last three years has found that almost half of such patients (48%) do not have ME/CFS. This is a reflection of the fact that there is no sensitive or specific diagnostic test (personal communication, Dr Gavin Spickett, Clinical Champion for the Northern Clinical Network Co-ordinating Centre (CFS/ME) Service, Newcastle Primary Care Trust).

A member of The Association of British Neurologists pointed out to NICE that: "***The importance of appropriate diagnosis of CFS/ME from common psychiatric conditions has not been mentioned even once***" (CG53 website).

In 2000 Anthony Komaroff, Professor of Medicine at Harvard and a world leader in ME/CFS, summarised the key areas in which ME/CFS differs from psychiatric illness in *The American Journal of Medicine*: "***Objective biological abnormalities have been found significantly more often in patients with (ME/CFS) than in the comparison groups. The evidence indicates pathology of the central nervous system and immune system. Autonomic nervous system testing has revealed abnormalities of the sympathetic and parasympathetic systems that are not explained by depression or physical deconditioning. Studies of hypothalamic and pituitary function have revealed neuroendocrine abnormalities not seen in healthy control subjects. There is considerable evidence of a state of chronic immune activation. In summary, there is now considerable evidence of an underlying biological process which is inconsistent with the hypothesis that (ME/CFS) involves symptoms that are only imagined or amplified because of underlying psychiatric distress. It is time to put that hypothesis to rest***". ("The Biology of the Chronic Fatigue Syndrome" *Am J Med* 2000;108:99-105).

The international medical and scientific literature is replete with evidence of the need to distinguish between ME/CFS and CFS/ME.



A clear message that emerged from the National Institutes of Health (NIH) State of the Science Conference on CFS held on 23<sup>rd</sup> – 24<sup>th</sup> October 2000 in Arlington, Virginia, was that CFS is a heterogeneous label and researchers **must** subgroup patients by features including chronicity, immunology and neuroendocrinology (Conference Calls for Serious Research. T Lupton. CFIDS Chronicle 2001:14:1:12-13).

In January 2001, experienced researchers and clinicians presented evidence of the urgent need for sub-grouping at the Fifth International AACFS Conference held in Seattle:

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

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

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

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

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

--- A large international multicentre study of autoimmunity was presented by E.Tan with (amongst others) participants from The Scripps Research Institute, La Jolla, California; the University of Washington; Harvard Medical School, Boston; State University of New York and George Washington University, Washington DC. This large study reflected the heterogeneity from one CFS centre to another and it emphasised the importance of sub-categorisation. This study of autoimmunity in ME/CFS showed the presence of autoantibodies to a particular cellular protein, MAP2, which is expressed primarily in neuronal cells. Autoantibodies directed at brain tissue could help explain some of the neurological and cognitive problems found in ME/CFS (<http://www.cfids.org/archives/2001/2001-2-article01.asp> ).

Previously, a 1996 paper from Tan et al demonstrated the occurrence of autoantibodies to a conserved intracellular protein (lamin B1), **which provides laboratory evidence for an autoimmune component in ME/CFS**. The authors found that 52% of patients with ME/CFS develop autoantibodies to components of the nuclear envelope (NE), mainly nuclear lamins, suggesting that in addition to the other documented disturbances of the immune system, humoral autoimmunity against polypeptides of the NE is a prominent immune derangement in ME/CFS. 67% of ME/CFS patients were positive for NE reactivity compared with 10% of normal subjects. No patients with either depression or atopy showed reactivity to NE proteins. Autoantibodies to NE proteins are relatively infrequent and most fall into the category of an unusual connective tissue disease subset characterised by brain or skin vasculitis (see “Autoantibodies to Nuclear Envelope Antigens in Chronic Fatigue Syndrome”. K Konstantinov, James Jones, Eng Tan et al. J Clin Invest 1996;98:8:1888-1896). Many patients with ME/CFS report a vasculitic-type headache which has become known as “the ME headache”. The paper concluded that such activation *“could be the result of various triggering agents, such as infections or environmental toxins”*. It recommended that: *“Future work should be directed at a better understanding of the autoimmune response of CFS patients to other NE antigens”*. This important paper has been widely cited in, for example: American Journal of Psychiatry:2003;160(2):221-236 (N Afari and D Buchwald); Clin Vaccine Immunol: 2002;9(4):747-752 (BH Natelson et al); Brain 2001;124(9):1821-1831 (RK Gherardi et al); Rheumatology: 2001;40(7):806-810 (M Nishikai et al) and Journal Watch:1997:314:4.

For reasons that do not stand up to scrutiny, the GDG refused to accept the 2003 Canadian Guidelines. This is both unreasonable and irrational, since the Canadian Guidelines separate ME/CFS from states of psychiatric fatigue (which the NICE Guideline does not) and was formulated by a group of expert clinicians who have examined and treated over 20,000 patients with ME/CFS. The Canadian Guidelines are vital to the greater understanding of ME/CFS as they provide a comprehensive assessment of the disorder.

The Canadian Guidelines may have been rejected by the GDG because those Guidelines specifically do not support the GDG's recommendation of CBT/GET: Dr Bruce Carruthers, Fellow of the Canadian Royal College and principle lead of the international expert team that produced the highly respected ME/CFS Clinical Case Definition, states in the Overview ( [http://www.mefmaction.net/documents/me\\_overview.pdf](http://www.mefmaction.net/documents/me_overview.pdf)):

***“A hypothesis underlying the use of Cognitive Behaviour Therapy (CBT) for ME/CFS is based on the premise that the patient’s impairments are learned due to wrong thinking and ‘considers the pathophysiology of CFS to be entirely reversible and perpetuated only by the interaction of cognition, behaviour, and emotional processes. The patient merely has to change their thinking and their symptoms will be gone. According to this model, CBT should not only improve the quality of the patient’s life, but could be potentially curative’. Supporters suggest that ‘ideally general practitioners should diagnose CFS and refer patients to psychotherapists for CBT without detours to medical specialists as in other functional somatic syndromes’. Proponents ignore the documented pathophysiology of ME/CFS, disregard the reality of patients’ symptoms, blame them for their illness and withhold medical treatment. Their studies have often included patients who have chronic fatigue but excluded more severe cases as well as those who have other symptoms that are part of the clinical criteria of ME/CFS. Further, their studies fail to cure or improve physiological impairments”.***

In this respect, it is notable that at the conference on “CFS” held on 28<sup>th</sup> April 2008 at The Royal Society of Medicine, psychiatrist Professor Peter White (lead adviser on “CFS” to the Department for Work and Pensions) put forward the argument that the less symptoms a definition of CFS has, the better. To back up his claim, and using a graph from a study by Professor Simon Wessely, White said: “*You notice a fairly straight line showing the more physical symptoms you have, the more likely you are to meet the criteria for psychiatric distress. The cut-off for CIS (Clinical Interview Schedule, revised in 1990 by psychiatrist Anthony Pelosi) for psychiatric morbidity is about 12. So once you get above 4 symptoms – you can see once you get 5,6,7,8 symptoms as the Canadian criteria suggest, you are more likely to find someone with a psychiatric disorder and not CFS/ME. So I would suggest you do not use the Canadian criteria*” (Co-Cure ACT: 1<sup>st</sup> July 2008).

Of particular concern is the fact that, despite paying lip-service to the need for correct assessment leading to correct diagnosis, the GDG specifically proscribes the investigations that would separate ME/CFS from behavioural disorders that come under the “CFS/ME” umbrella.

Influenced by the psychiatric lobby, the GDG ignored these important issues and produced a Guideline that failed to identify those with ME/CFS and failed to distinguish them from those suffering from psychiatric states of medically unexplained chronic fatigue (i.e. from somatoform disorder).

Commenting on the final Guideline, one GP from Bath said: “*The NICE Guidelines make it more difficult, instead of separating ME from other illnesses with fatigue, NICE is just broadening the umbrella. Now fatigue and sore throat is enough to have ME. ME patients, and especially patients who don’t have ME but will be labelled as ME patients, will suffer as a consequence*” (Dr Andrew Ashley, eBMJ, 6<sup>th</sup> September 2007).

A 2005 Report from the ME Alliance (encompassing six UK charities) “ME Diagnosis: Delay Harms Health” states: “*While we can be certain that around 25,000 people per year will develop ME/CFS, the likelihood is that the real figure is very much larger, possibly in the region of 50,000*”. The reference cited for this statement is “Incidence of fatigue symptoms and diagnoses presenting in UK primary care from 1990 to 2001”. Gallagher AM, Thomas JM, Hamilton WT, White PD. JRSM 2004;97:571-575.

In the UK, there are five times more people with ME/CFS than there are with HIV AIDS.

These are disturbing figures, so it is imperative that bodies such as NICE provide correct information to aid diagnosis and management. In its Clinical Guideline 53, NICE failed to do so.

The consequences of misdiagnosis and the imposition of inappropriate management regimes are extremely serious, but far from serving as an aid to diagnosis, the Guideline has merely continued and confounded the existing confusion.

## 2. Failure to accept the national and international classification codes

Correct classification of a disorder does matter because it defines medical understanding and treatment of a disorder; it also impacts upon NHS service provision and upon the delivery of appropriate and necessary medical care. It is the case that software systems in the NHS use ICD codes to encode diagnostic data; for this reason alone, ICD codes matter very much.

The WHO has classified ME as a neurological disorder since 1969.

The UK Read Codes used by all GPs classify ME/CFS as a neurological disorder (F286).

The UK National Service Framework (NSF) includes ME/CFS as a long-term neurological disorder.

The Department of Health accepts both the neurological classification of the disorder and that the disorder is indeed neurological.

NICE itself correctly categorises ME/CFS according to the WHO international classification as a neurological disorder (see: [www.nice.org.uk/nicemedia/pdf/CG53AuditCriteria.doc](http://www.nice.org.uk/nicemedia/pdf/CG53AuditCriteria.doc)).

Although the Guideline acknowledges the WHO classification, there is disparity between NICE itself and the CG53 Guideline Development Group: the consensus of the GDG members does not accept the neurological status of CFS/ME: *“The WHO classifies CFS/ME as a neurological illness and some members of the GDG felt that the guideline should recognise this classification. Others felt that to do so did not reflect the nature of the illness, and risked restricting research and future treatments for CFS/ME”* (52 page version, page 4).

In rejecting the formal classification, the GDG members are following in the recent tradition of such bodies as the Medical Research Council (MRC), which incorrectly categorises ME/CFS as a mental disorder (see the MRC Mental Health Scoping Study Report from the Strategy and Portfolio Overview Group of January 2005: 6.2: *“Mental health research in this instance covers CFS/ME”*); NHS Plus; the NHS Information Authority; the Joint Royal Colleges of Physicians, General Practitioners and Psychiatrists; the Royal Society of Medicine (despite it having accepted ME as a distinct entity in 1978) and the Royal College of Paediatrics and Child Health. All these organisations support the psychosocial model of “CFS/ME” and do not subscribe to the view that ME/CFS is a neurological disorder, preferring instead the Oxford-defined “CFS” which is classified under Mental Health (WHO ICD-10: F48.0), into which broad category they have subsumed the discrete disorder ME. It is a matter of record that the intention of the Wessely School is to “eradicate” ME as a nosological entity ([http://www.meactionuk.org.uk/Quotable\\_Quotes\\_Updated.pdf](http://www.meactionuk.org.uk/Quotable_Quotes_Updated.pdf)).

It should be noted that the Guideline refers to the WHO classification as a *“neurological illness”* whereas the WHO itself uses the term “disease”: this is highly significant because the psychiatric lobby that selected and advised the GDG believe that “disease” is the only objective, medically diagnosable pathology and that **“illness is a behaviour”**. In 2005 the UnumProvident Centre for Psychosocial and Disability Research

at Cardiff University produced "The Scientific and Conceptual Basis of Incapacity Benefits" written by Waddell and Aylward and published by The Stationery Office. This promotes the psychosocial model of all "illness", stating that benefit trends are a social cultural phenomenon, rather than a health problem and states on page 123: "*The solution is not to cure the sick but a fundamental transformation in the way society deals with sickness and disabilities. The goal and outcome of treatment is work*". This is the very ethos that underpins the GDG's management recommendation of behavioural interventions and aerobic exercise.

NICE has confirmed that the Guideline is entirely the responsibility of the GDG, with the result that the final Guideline failed to accept the correct classification code and thus the correct disease status of ME/CFS.

### 3. Failure to consider the existing evidence-base of knowledge about the disorder under review.

Before producing a Guideline such as CG53, the GDG members needed to acquaint themselves fully with the body of existing knowledge about the disorder, yet in this case they did not do so, asserting that consideration of the aetiology was not in their remit. Since their remit was to produce an aid to diagnosis, this is illogical, because consideration of the existing body of knowledge does not automatically include consideration of aetiology.

Examples of this existing evidence-base that would assist diagnosis of ME/CFS but which the GDG chose to ignore are set out in a 174 page document entitled "Illustrations of Clinical Observations and International Research Findings from 1955 to 2005 that Demonstrate the Organic Aetiology of Myalgic Encephalomyelitis / Chronic Fatigue Syndrome" by Professor M Hooper et al. That document is available online at [http://www.meactionuk.org.uk/Organic\\_evidence\\_for\\_Gibson.htm](http://www.meactionuk.org.uk/Organic_evidence_for_Gibson.htm) .

This evidence-base makes it plain that ME/CFS patients are extremely sick.

In November 2006, the US Centre for Disease Control (CDC) announced its "CFS Toolkit" to inform not just the US but the whole world about the nature and severity of ME/CFS.

The following are extracts from the Press Conference:

Dr Julie Gerberding, Director of the US CDC: "*One of the things that CDC hopes to do is to help patients know that they have an illness that requires medical attention, but also to help clinicians be able to understand, diagnose and help people with the illness. **But more importantly, to be able to validate and understand the incredible suffering that many patients and their families experience in this context. We are committed to improving the awareness that this is a real illness and that people need real medical care and they deserve the best possible help that we can provide. The science has progressed (which has) helped us define the magnitude and understand better the clinical manifestations (and this has) led to a sorely needed foundation for the recognition of the underlying biological aspects of the illness. We need to respect and make that science more visible. I have heard from hundreds and hundreds of people who are telling their stories – their courage, their commitment to try to live the best possible life they can (and) the tremendous impact that this is having on their ability to function***".

Dr William Reeves, Chief of Chronic Viral Diseases Branch at CDC: "***We've documented, as have others, that the level of impairment in people who suffer from (ME)CFS is comparable to multiple sclerosis, AIDS, end-stage renal failure, chronic obstructive pulmonary disease. The disability is equivalent to that of some well-known, very severe medical conditions. We found that (ME)CFS follows a pattern of remitting and relapsing symptoms, the symptoms can change over time, and that spontaneous recovery is rare. We found that the best predictor for (ME)CFS was intensity of the initial infectious disease. The sicker the patient when s/he first got infected, the more likely they were to have persisting chronic symptoms. There were no other factors, psychological or biological, that held up under thorough analysis***".

Professor Anthony Komaroff of the Harvard Medical School: ***“There are now over 4,000 published studies that show underlying biological abnormalities in patients with this illness. It’s not an illness that people can simply imagine that they have and it’s not a psychological illness. In my view, that debate, which was waged for 20 years, should now be over. A whole bunch of studies show that the hormone system is different in patients with (ME)CFS than in healthy people, people with depression and other diseases. Brain imaging studies have shown inflammation, reduced blood flow and impaired cellular function in different locations of the brain. Many studies have found that the immune system appears to be in a state of chronic activation (and) genes that control the activation of the immune system are abnormally expressed in patients with this illness. A number of studies have shown that there probably are abnormalities of energy metabolism in patients with this illness”.***

During the Question and Answer session, the question was asked: *“You’ve cited quite a bit of research that validates that (ME)CFS is actually a real disease. Why is there still such a level of scepticism in the medical community? Is it simply a lack of awareness among health professionals?”*

Komaroff replied: *“There are an awful lot of sceptics I’ve met who really just haven’t read the research literature (and) don’t even know there are 4,000 peer-reviewed published papers out there. I think that’s probably the biggest factor, combined with the fact that those people took a stand early on as to what they believe and have been reluctant to back off”.*

Professor Nancy Klimas, Professor of Medicine, University of Miami: ***“I’ve treated over 2,000 (ME)CFS patients. Today, there is evidence of the biological underpinnings. And there’s evidence that the patients with this illness experience a level of disability that’s equal to that of patients with late-stage AIDS, patients undergoing chemotherapy, patients with multiple sclerosis. And that has certainly given it a level of credibility that should be easily understood. There are diagnostic criteria that enable clinicians to diagnose (ME)CFS in the primary care setting”.***

The full Press Conference transcript is available at:

<http://www.cdc.gov/od/oc/media/transcripts/t061103.htm?id=36410>

All this information (and more) was submitted to the GDG by medical practitioners, by medical researchers, by ME charities, by patients, by carers and by Members of Parliament. Indeed, NICE received so much evidence (sometimes sent by Recorded Delivery, such was the desperation of patients to ensure that it arrived safely) and so many submissions of concern about this particular Guideline that the original publication date had to be deferred from April 2007 to 22<sup>nd</sup> August 2007. Despite this, much of the submitted evidence was disregarded by the GDG.

If a medical practitioner disregards medical evidence and fails to keep up-to-date with progress in medical science, it could be said to be negligent, but for the GDG intentionally to disregard the body of existing knowledge and to act as if this body of medical knowledge does not exist (as the GDG did because members were instructed to do so – see below) is acting directly against the best interests of patients and as such is surely professional misconduct.

Further, for the GDG to recommend as the only form of management psychotherapy techniques that are designed to disabuse patients of their legitimate belief that they have a serious organic illness and instil the belief that they have a condition from which they can recover if they are willing to partake in aerobic exercise has rightly caused offence and outrage across UK society, including medical and scientific communities and Members of Parliament.

### **Failure to offer guidance on symptom management**

An attempt to describe the devastating effects of ME/CFS was made in 1995 at a US Congressional Briefing by Professor Mark Loveless, Head of the AIDS and CFS Clinic at Oregon Health Sciences University. He told Congress that an ME/CFS patient ***“feels effectively the same every day as an AIDS patient feels two weeks before death --- the only difference is that in ME/CFS, the symptoms can go on for decades”.***

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

The GDG was selective in its acceptance of the documented signs and symptoms seen in ME/CFS (for a list of documented signs, see below).

ME/CFS causes impaired mobility and disability in all cases. The degree of impairment and complexity depends on the degree of diffuse brain injury and end organ involvement. ME/CFS is a relapsing / remitting disease, with new symptoms occurring either in relapses or slowly accruing over time. Between relapses, symptoms may improve with sufficient rest, but permanent neurological problems often persist, especially as the disease advances.

The pathognomonic features of ME/CFS are:

- generalised or localised muscular fatigue after minimal exertion, often involving severe myalgia, with prolonged recovery time (this is the “sheet-anchor” of the diagnosis)
- neurological disturbance, especially of cognitive, autonomic and sensory functions
- variable involvement of cardiac and other systems
- an extended relapsing course
- marked variability of symptoms (<http://www.cfs-news.org.me#taskforce>).

At the Royal Society of Medicine meeting on 28<sup>th</sup> April 2008 on “CFS” referred to above, Professor Peter White advised that once a patient has more than four symptoms, it was likely that s/he had a psychiatric disorder.

Such a belief is not in accordance with the British Medical Association’s advice on complex disorders. The Foreword to The British Medical Association Complete Family Health Guide is clear: *“The Complete Family Health Guide is based on advice from a panel of medical consultants chosen by the BMA, and their experience provides an unrivalled assurance of quality and reliability”*. Under hyperthyroidism, 10 symptoms are listed; under Cushing’s syndrome, 11 symptoms are listed; under asthma, 11 symptoms are listed; under chronic kidney failure, 8 symptoms are listed; under AIDS, 13 symptoms are listed. The unproven beliefs of the psychiatric advisers to the GDG have no relevance in complex disorders such as ME/CFS.

Failure by the GDG to acknowledge the existence of the cardinal symptoms of ME/CFS means that the Guideline fails to offer the correct advice to GPs about symptom recognition and management, which is a failure of its remit. For example, in addition to post-exertional muscular fatigue, there is extreme malaise with nausea, often accompanied by a vice-like myalgia; abdominal pain and diarrhoea; frequency of micturition with nocturia; photophobia; visual problems; hyperacusis; loss of balance; dizziness, including frank vertigo; spatial disorientation; ataxia; inability to sustain muscle strength, as in peeling vegetables or drying oneself or even holding up one’s head unsupported; neuromuscular incoordination, involving not only fine-finger movement but also the larynx – a frequent complaint is the need to swallow carefully to avoid choking; symptoms of hypovolaemia, with blood pooling in the legs – the patient feels faint due to insufficient blood supply to the brain; episodes of *angor animi* (brought about by abrupt vasomotor changes that cause the patient to have uncontrollable shaking, like a rigor, and to think they are at the point of death: such attacks cause understandable terror in patients and they increase in frequency as the disease progresses); shortness of breath on minimal exertion; intermittent chest pain akin to myocardial infarction; segmental chest wall pain; vascular spasms; vasculitic rashes (cutaneous vasculitis), and intolerance to alcohol and medication, a feature that the renowned neurologist Professor Charles Poser of Harvard described as pathognomonic at the 1994 Dublin International Symposium held under the auspices of the World Federation of Neurology.

Such symptoms are not found in “chronic fatigue”.

### **Failure to offer appropriate guidance on management / rehabilitation strategies**

By the deliberate exclusion from consideration of the existing evidence-base on ME/CFS, the inherent dangers of an inappropriate management regime are legion.

The draft Guideline of September 2006 stated: “*When the adult or child’s main goal is to return to normal activities then the therapies of first choice should be CBT or GET*” (6.3.6.3) and continued at 6.3.6.19: “*If agreed GET goals are met, exercise duration and intensity can be increased if the patient would like to progress further*”. This statement caused offence both to patients with ME/CFS (who are desperate to return to normal activities and to progress further) and to those medical professionals who do not subscribe to the psychiatric model of the disorder, so it was removed from the final Guideline, but the underlying ethos (i.e. that “CFS/ME” is a somatisation disorder that must be managed by CBT and graded exercise) remains and has been the major cause of rejection of the Guideline by patients and professionals alike, as well as most of the UK ME/CFS charities.

On 18<sup>th</sup> November 1995, Anthony Komaroff, Professor of Medicine at Harvard, went on record in his London lecture: “*Not once has anyone’s illness gone away with psychiatric therapy*”. Thirteen years later, that remains true.

The ME Association does not endorse any form of behaviour treatment for people with ME/CFS (ME Essential: April 2008: 10-12) and disagrees strongly with the GDG’s management recommendation for both CBT and GET.

### **Definitions of CBT and GET**

A key issue is how GET is defined: it may encompass anything from gentle stretching exercises to rigidly controlled incremental aerobic exercise. No-one could legitimately object to the former, but in the NICE Guideline, **the recommended graded exercise plan specifies that the intensity of GET should be incrementally increased (with the patient’s agreement), leading to aerobic exercise.**

This is in direct contradiction to international ME/CFS experts such as Professor Paul Cheney from the US, who in 1999 explained why aerobic exercise should not be used: “*The most important thing about exercise is not to have them do aerobic exercise. I believe that even progressive aerobic exercise, especially in phase one and possibly in other phases, is counter-productive. If you have a defect in the mitochondrial function and you push the mitochondria by exercise, you kill the DNA*” (Lecture given in Orlando, Florida, February 1999, at the International Congress of Bioenergetic Medicine, audiotape #2).

In that workshop, Cheney discussed the damage done to the mitochondria, which he said was “*substantial*”, and he referred to the loss of mitochondria as the endpoint of this disease.

Cheney’s findings were supported by Benjamin Natelson, Professor of Neurology at New Jersey Medical School: in his 1999 lecture in the UK (at The Fatigue 2000 Conference held in April in London), Natelson discussed his work on muscle metabolism using NMR (nuclear magnetic resonance) testing the muscle of patients with ME/CFS after exercise, in which his team demonstrated a problem with mitochondrial recovery (Conference reported in the ME Association Newsletter: Perspectives, Summer 1999: 18).

There is a significant literature on mitochondrial defects (structural and functional) in ME/CFS which the GDG simply ignored, preferring instead to recommend behavioural interventions such as GET that is designed to improve patients’ alleged deconditioning brought about by alleged disuse.

The second edition of the Guide to Mental Health in Primary Care (originally produced in 2000 under the auspices of the World Health Organisation’s Mental Health Collaborating Centre at the Institute of Psychiatry, London) defines CBT in the following terms: “*This is used to change a patient’s thought processes and behaviour in order to bring about relief of symptoms. (It) includes challenging irrational beliefs, replacing the irrational beliefs with alternative ones*”.

In 2002, the UK Chief Medical Officer's Working Group Report on "CFS/ME" defined CBT as "*a tool for constructively modifying attitude and behaviour*" (Annex 6, page 8).

The Medical Research Council's (MRC) current PACE Trial Identifier into the efficacy of CBT and GET for people with "CFS/ME" (which by definition excludes those with ME/CFS, as it uses the Oxford criteria --- see below) states that GET "*will be based on the illness model of both deconditioning and exercise avoidance*" and that CBT "*will be based on the illness model of fear avoidance*". The Principal Investigators (PIs) for MRC trials of CBT and GET are Wessely School psychiatrists (i.e. the same psychiatrists who compiled the Oxford criteria, some of whom acted as advisers to the York Review team upon whose Systematic Review the GDG relied). It is notable that the Trial Identifier states about the Oxford criteria: "*We chose these broad criteria in order to enhance recruitment*" (PACE Trial Identifier: 3.6).

The NICE Guideline uses this same (psychosocial as distinct from biomedical) model of "CFS/ME", placing emphasis on patients' "faulty belief system" that can be "corrected" by CBT and aerobic exercise.

The NICE Guideline stipulates the mass application of its recommended psychiatric management regime for all patients with mild to moderate ME/CFS, and an adapted regime of the same nature for those severely affected and for children. The GDG chose to dismiss the submitted evidence that people with mild to moderate ME/CFS have been made worse by GET and have become severely affected, with disastrous and life-long consequences.

Moreover, even though the NSF (launched on 10<sup>th</sup> March 2005, well before the publication of the "CFS/ME" Guideline on 22<sup>nd</sup> August 2007) states: "***Random controlled trials are not necessarily best suited to research questions involving long-term outcomes, varied populations with complex needs and assessment of impact on quality of life rather than a cure***", the GDG ignored this dictum and inappropriately chose to rely only on RCTs, which is contravention of the AGREE Instrument to which NICE subscribes.

#### The York Systematic Reviews of the literature on CBT/GET

In its recommendation of behavioural interventions as the primary management strategy for people with "CFS/ME", the GDG placed undue reliance on the revised Systematic Review of the literature on CBT and GET carried out by the Centre for Reviews and Dissemination (CRD) at the University of York ("The diagnosis, treatment and management of Chronic Fatigue Syndrome (CFS) / Myalgic Encephalomyelitis (ME) in adults and children. Work to support the NICE Guidelines"; Anne-Marie Bagnall, Susanne Hempel, Duncan Chambers, Vickie Orton and Carol Forbes; October 2005).

This was a revision of a review of the literature on the alleged benefits of CBT/GET carried out in 2001 by the same review team ("Interventions for the Treatment and Management of Chronic Fatigue Syndrome – A Systematic Review". Whiting P, Bagnall A-M et al. JAMA 2001;286:1360-1368). Of note is that fact that concerns expressed by the same review team in the 2001 JAMA review were excluded from the 2005 review (i.e. from the review that was done specifically to support the work of NICE), with the result that CBT/GET appeared in a better light than in the 2001 review of essentially the same literature.

The 2005 revision was itself subsequently revised and published in The Journal of the Royal Society of Medicine as "Interventions for the treatment, management and rehabilitation of patients with chronic fatigue syndrome / myalgic encephalomyelitis: an updated systematic review": Chambers D, Bagnall A-M, Hempel S, Forbes C; JRSM 2006;99:506-520).

**The revised systematic review (2005) asserts: "*graded activity is normally considered an integral part of CBT for CFS/ME*"** (full Guideline page 51). This is not the case, and prominent American researchers take a different approach, but **this assertion encapsulates the approach recommended by the GDG.**



The Systematic Review team at York identified only three RCTs of GET for inclusion in the draft Guideline, with a further two RCTs of GET included in the final Guideline, making a grand total of five RCTs of GET.

Of the five studies of GET in the York Reviews, three used the Oxford (1991) criteria which, by their own definition, exclude those with a neurological disorder (and ME/CFS is classified as a neurological disorder). This means that no patient with ME/CFS (as distinct from “medically unexplained chronic fatigue”) should have been included in those studies that used the Oxford criteria.

Of significance is the fact that the Oxford definition expressly includes patients with somatisation disorders and those with personality disorders, these being mental illnesses which may be perpetuated by aberrant illness beliefs and by the misattribution of normal bodily sensations, and patients with such illnesses may be seeking to obtain secondary gain by the adoption of the sick role, all being charges made in the UK medical literature about patients with ME/CFS. ME/CFS is not a mental disorder.

The five trials totalled just 426 patients out of a UK ME/CFS population of 240,000 (the figure of 240,000 is given in the Chief Medical Officer’s Working Group Report of January 2002 but this figure has been disputed on the basis that it may include those with “chronic fatigue” as distinct from those with ME/CFS).

Nevertheless, 426 patients is a statistically insignificant figure on which to predicate a national policy, especially since the number of patients within the cohort who specifically had ME/CFS was unknown.

It becomes even less significant if one considers only those trials that used the CDC Fukuda 1994 criteria as distinct from the 1991 Oxford criteria: one trial (Wallman et al) had 61 subjects and the other trial (Moss-Morris et al) had just 49 subjects, making a total of 110 patients, which is 0.046% of 240,000 patients (and once again it is not determined if any of the subjects had ME/CFS as distinct from CFS/ME).

That the Oxford criteria do indeed exclude those with ME/CFS was confirmed by one of the authors of those criteria, Professor Anthony David from The Institute of Psychiatry, London: ***“British investigators have put forward an alternative, less strict, operational definition which is essentially chronic fatigue in the absence of neurological signs, with psychiatric symptoms as common associated features”***. (“Postviral fatigue syndrome and psychiatry” AS David. British Medical Bulletin 1991:47:4:966-988).

The Oxford 1991 criteria state that the authors were looking at patients *“with a principal complaint of disabling fatigue”* and that *“the aim of the meeting was to seek agreement amongst research workers for future studies of patients with chronic fatigue”* (“A report – chronic fatigue syndrome: guidelines for research”. MC Sharpe, A David, S Wessely et al. JRSM 1991:84:118-121).

Unsurprisingly, given that the Oxford 1991 criteria exclude those with neurological disorders, the key symptomatology of ME/CFS is excluded, yet the NICE GDG claims to be including “ME” in their term “CFS/ME”. The GDG clearly cannot be looking at ME/CFS patients when the cardinal features of the disorder are specifically excluded from the case definition used by the three of the five studies upon which the GDG relied to support its recommendation of the national implementation of incremental aerobic exercise.

In March 2005, Susanna Agardy from Australia pointed out that: *“The definition in the Oxford Criteria for CFS does not include post-exertional malaise. Where selection of subjects ignores and excludes post-exertional malaise (as with the use of the Oxford criteria), the experimenters’ belief system is perpetuated and remains unchallenged”* (Co-Cure RES: 31<sup>st</sup> March 2005).

In a keynote lecture at the ME Research UK international research conference held on 25<sup>th</sup> May 2007 in Edinburgh, a psychiatrist with a dedicated ME/CFS practice, Dr Eleanor Stein from Canada, denounced the Oxford criteria, which she said *“could describe almost anybody. I do not believe that studies which use the Oxford criteria can be generalised to patients with ME/CFS”*. She also said it is very clear that ME/CFS patients have *“a host of physiological abnormalities that cannot be explained by psychiatric, attitudinal or behavioural hypotheses”*. Stein was outspoken: ***“I would never in my practice use the Wessely model of***

*cognitive therapy. I find it disrespectful to try to convince somebody they don't have an illness that they clearly have”.*

### **Evidence of concern about the RCTs of GET upon which the GDG relied**

As set out in the Hooper & Reid Report of January 2006 “Inadequacy of the York [2005] Systematic Review of the Evidence Base” ([http://www.meactionuk.org.uk/FINAL\\_on\\_NICE\\_for\\_Gibson.html](http://www.meactionuk.org.uk/FINAL_on_NICE_for_Gibson.html)), substantial concern about this alleged “evidence-base” existed well before publication of the final Guideline. Although pointed out to the GDG, this legitimate concern was ignored.

Hooper & Reid drew attention to the fact that much of the negative comment contained in the first Systematic Review of the literature on the effectiveness of CBT/GET (published in JAMA 2001) simply disappeared from the 2005 revision of that Review by the same authors that was carried out specifically to support the work of NICE.

For example, in the 2001 version, attention was drawn to the high drop-out rates in trials of GET, but this was missing from the 2005 version. In one of just five GET RCTs (Wearden et al, 1998) over one third (36%) dropped out of the treatment arm. In the 2001 version, the review team stated: “*The highest drop-out rates were in the behavioural interventions*” and: “*When deciding what treatments should be given to patients, it is important to take adverse effects, especially those which are so severe as to cause patients to discontinue treatment, into consideration*” but both these statements were omitted from the 2005 version.

Regarding effectiveness of the intervention, the 2001 version stated: “*An objective measure of the effect of any intervention would be whether participants have increased their working hours, returned to work or school, or increased their physical activities*” but this was missing from the 2005 version, probably because there is no objective evidence whatever that GET is effective.

A review team charged with ascertaining the efficacy and safety of the recommended interventions might have been expected to show more concern about a drop-out rate of 40%. If the number of people who were approached but who refused to enter the trials is included, the combined refusal / drop-out rate mounts to 50.66%.

One part of the remit of the York review team was to determine “*How effective and safe are interventions for the treatment and/or management of CFS/ME in adults and children?*” but the reviewers demonstrated no concern about the high drop-out rate, and there is no risk-benefit analysis.

No consideration seems to have been given to the international concerns about GET, for example:

#### United States:

“*Our reluctance to endorse graded activity arises from our vastly different clinical experience in the US*” (“Understanding Chronic Fatigue Syndrome”. Friedberg F, Jason LA. American Psychological Association, Washington, 1998).

“*Our clinical experience suggests that graded exercise / CBT for clients who do not exhibit fear-based avoidance may be counter-productive and trigger symptom flare-ups*” (Fred Friedberg, Leonard A Jason, J Clin Psychol 2001;67:433-455).

Jason is the author quoted frequently by the Review team (Bagnall et al), yet she failed to mention his reservations about GET.

Canada:

*“Exercise programmes must be entered into cautiously as clinical studies have indicated that symptoms worsened in approximately half of the ME/CFS patients”* (Canadian National Guidelines).

Australia:

*“Many (CBT/GET) studies have significant refusal and drop-out rates, which may reflect on the acceptability of the treatment regimens”* (Australian National Guidelines).

Bagnall et al list both the Canadian and Australian guidelines amongst their references, yet they fail to mention the clear concerns.

New Zealand:

*“GET may cause relapses and is therefore potentially harmful”* (New Zealand Guidance Group).

All critical comment about GET, no matter how eminent the source, was excluded by Bagnall et al from the 2005 version that was prepared to support the work of NICE.

A striking omission from the 2005 version was the failure to cite the reviewers’ own work that had been published in JAMA in 2001, which is one of the world’s most prestigious medical journals. For some reason, in 2005 Bagnall et al disowned their own 2001 article, making no reference to it.

This gave rise to the possibility that Bagnall et al were subjected to covert external influence in the review they prepared to support the work of NICE.

It would be most unfortunate if a powerful outside influence has been able to impose its own concepts and requirements on a team of supposedly neutral reviewers, but there is abundant evidence that someone prevailed upon Bagnall et al to dilute and delete opinions held in 2001 on the same corpus of research.

**Contra-indications to the use of GET in ME/CFS that the GDG chose to ignore**

Whilst there was indeed a paucity of RCTs of GET in ME/CFS, there was nevertheless an abundance of published evidence on the documented abnormalities in ME/CFS that would, had it been considered by the GDG, have informed their opinion about the nature of the disorder under consideration and should have caused them to consider the suitability of recommending incremental aerobic exercise for such patients.

For the most part, many patients with ME/CFS are far too sick to take part in incremental aerobic exercise.

The striking variability of their symptoms means that they cannot know from one minute to the next whether or not they will suddenly feel intensely ill, become incapacitated and be at the point of collapse.

At her In-coming IACFS Presidential Address in March 2005, Nancy Klimas, Professor of Medicine at the University of Miami and perhaps the world’s leading authority on ME/CFS, said: ***“Our patients are terribly ill, misunderstood, and suffer at the hands of a poorly informed medical establishment”*** (<http://www.co.cure.org>).

Equally important is the established fact that cardiac output does not meet metabolic demand, even at minimal exertion, let alone during incremental aerobic exercise. ***“The cardiac index of ME/CFS patients is so severe that it falls between the value of patients with myocardial infarction and those in shock”*** (Professor Paul Cheney; IACFS, Florida, January 2007).

### Expert Patient evidence

Although the Government is promoting its “Expert Patient” programme as the way forwards, the GDG dismissed and ignored the evidence provided by patients who have become expert in managing their own condition.

Surveys of almost 5,000 patients carried out by UK ME/CFS charities have shown unequivocally that GET is unacceptable and can be actively harmful.

Those surveys include one sponsored jointly by the ME Association and Action for ME (“Report on a Survey of Members of Local ME Groups”. Dr Lesley Cooper, 2000). It found the high numbers of long-term sufferers to be significant (75% had been ill between 3 and 15 years, with 18 having been ill over 20 years, which differs from the survey analysed in July 2000 by The 25% ME Group for the Severely Affected, which found that 68 out of 206 respondents had been ill for over 15 years). Cooper found that “*Graded exercise was felt to be the treatment that made more people worse than any other (39%)*” and that it had actually harmed patients (<http://www.afme.org.uk/res/img/resources/Group%20Survey%20Lesley%20Cooper.pdf>).

Another survey of 2,338 ME/CFS sufferers (“Severely Neglected: M.E. in the UK”) was carried out in 2001 by Action for ME; its preliminary report stated: “*Graded exercise was reported to be the treatment that had made most people worse*”; in the final report, this was changed to stating that graded exercise had made 50% of patients worse (<http://www.afme.org.uk/res/img/resources/Severely%20Neglected.pdf>).

The 25% ME Group for the Severely Affected carried out a further survey in 2004 which found that 93% of 437 respondents found GET to be unhelpful, with a shocking 82% reporting that their condition was made worse by GET

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

In 2005, a 42 page report of a survey of children and young people (“Our Needs, Our Lives”) published by The Young ME Sufferers Trust found that 88% had been made worse by exercise

(<http://www.tymestrust.org/pdfs/ourneedsourlives.pdf>).

All these surveys pre-date the publication of the NICE Guideline, but evidence continues to mount that GET is harmful. Since August 2007, Action for ME has published another survey of over 2,760 patients (“M.E. 2008: What progress?”) which found that one third had been made worse by GET and that at their worst, 88% were bed/housebound, being unable to shower, bathe or wash themselves, and that 15% were unable to eat unaided. The Press Release stated: “*Survey finds recommended treatment makes one in three people worse*” (<http://www.afme.org.uk/res/img/resources/Survey%20Summary%20Report%202008.pdf>).

The ME Association is currently conducting the largest ever survey and the preliminary results show that 44.9% were made worse by GET and that GET is unacceptable to 57.1 % of patients (personal communication, Dr Charles Shepherd, Medical Adviser, The ME Association).

One ME/CFS sufferer who has been ill for almost three decades correctly encapsulated the patients’ perspective: after just 20 minutes of normal activity, “*my legs were rubber, my heart was pounding, my chest tight, pain was excruciating – legs, back, shoulder, neck. My legs remained unstable. I was forced to spend much time in bed. Over-exercising can have dire consequences. Refusal to do so is not simply fear-based – it is rational. People with ME/CFS who avoid over-doing things are not defeating their treatment protocols; they are in a subgroup in which exercise beyond tolerance should not be part of the protocol in the first place. If I exercise as directed and get an agonising flair of a week’s duration, it would be irrational of me to do that again. I am not being resistant to treatment – I am an example of the fact that some treatment protocols are inappropriate*” (Jim Roache. Co-Cure MED: 26 November 2004).

Whilst certain UK psychiatrists readily ascribe such symptoms to de-conditioning, numerous published studies confirm that there is no evidence of de-conditioning in ME/CFS patients (see below).

Documented pathology seen in ME/CFS that contra-indicates GET which was ignored by the GDG

According to Professor Nancy Klimas, ME/CFS can be as severe as congestive heart failure and the most important symptom of all is post-exertional relapse. Although this was said at the ME Research UK international conference held in Cambridge in May 2008 (i.e. after the publication of the NICE Guideline), published evidence of this has been in the literature for over two decades, but the GDG chose to ignore it.

In 1983, UK researchers documented evidence of a consistent pattern of complexity, including “*malaise, exhaustion on physical or mental effort, chest pain, palpitations, tachycardia, polyarthralgia, muscle pains, back pain, true vertigo, dizziness, tinnitus, nausea, diarrhoea, abdominal cramps, epigastric pain, headaches, paraesthesiae and dysuria*” (Keighley and Bell, JRCP: 1983:339-341).

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

In 1985, UK researchers demonstrated muscle abnormalities in ME/CFS patients: “*The post-viral fatigue syndrome, also known as ME, has been recognised recently as a distinct neurological entity with increasing evidence of the organic nature of the disease. The most important findings were type II fibre predominance, subtle and scattered fibre necrosis and bizarre tubular structures and mitochondrial abnormalities. About 75% of the patients had definitely abnormal single fibre electromyography results*” (Goran A Jamal Stig Hansen JNNP 1985:48:691-694).

In 1987, Archer demonstrated that: “**Relapses are precipitated by undue physical or mental stress. However compelling the evidence for an hysterical basis may be, there is further, equally compelling, evidence of organic disease. Some patients do have frank neurological signs. Muscle biopsies showed necrosis and type II fibre predominance**” (JRCP: 1987:37:212-216).

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

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

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

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

In 1990, a UK researcher pointed out the folly of CBT/GET: “*It has been suggested that a new approach to the treatment of patients with postviral fatigue syndrome would be the adoption of a cognitive behavioural model*” (Wessely S, David A et al. JRCP 1989:39:26-29). **Those who are chronically ill have recognised**

*the folly of the approach and, far from being maladaptive, their behaviour shows that they have insight into their illness” (D O Ho-Yen JRCGP 1990:40:37-39).*

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

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

In 1992, US researchers (including Robert Gallo, the co-discoverer of the HIV virus) found that **“57% of patients were bed-ridden, shut in or unable to work. Immunologic (lymphocyte phenotyping) studies revealed a significantly increased CD4 / CD8 ratio. Magnetic resonance scans of the brain showed punctate, subcortical areas of high signal intensity consistent with oedema or demyelination in 78% of patients. Neurologic symptoms, MRI findings, and lymphocyte phenotyping studies suggest that the patients may have been experiencing a chronic, immunologically-mediated inflammatory process of the central nervous system”** (A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpes Type 6 infection. Dedra Buchwald, Paul Cheney, Robert Gallo, Anthony L Komaroff et al Ann Intern Med 1992:116:2:103-113).

Also in 1992, the US Department of Health and Human Services produced a pamphlet on ME/CFS for the guidance of physicians (NIH Publication No. 92-484) which stated: **“ME/CFS symptoms overlap with those of many well-recognised illnesses, for example, lupus erythematosus (SLE) and multiple sclerosis. Psychiatric evaluations fail to identify any psychiatric disorders. Many people with ME/CFS have neurologic symptoms, including paresthesias, dysequilibrium and visual blurring. A few patients have more dramatic neurologic events such as seizures, periods of severe visual impairment, and periods of paresis. Evidence suggests that several latent viruses may be actively replicating more often in (ME)CFS patients than in healthy control subjects. Most investigators believe that reactivation of these viruses is probably secondary to some immunologic challenge. It is important to avoid situations that are physically stressful”**.

On 18<sup>th</sup> February 1993, Professor Paul Cheney testified before the US FDA Scientific Advisory Committee as follows: **“I have evaluated over 2,500 cases. At best, it is a prolonged post-viral syndrome with slow recovery. At worst, it is a nightmare of increasing disability with both physical and neurocognitive components. The worst cases have both an MS-like and an AIDS-like clinical appearance. We have lost five cases in the last six months. The most difficult thing to treat is the severe pain. Half have abnormal MRI scans. 80% have abnormal SPECT scans. 95% have abnormal cognitive-evoked EEG brain maps. Most have abnormal neurological examination. 40% have impaired cutaneous skin test responses to multiple antigens. Most have evidence of T-cell activation. 80% have evidence of an up-regulated 2-5A antiviral pathway. 80% of cases are unable to work or attend school. We admit regularly to hospital with an inability to care for self”**.

Also in 1993, Professor Anthony Komaroff from Harvard published his **“Clinical presentation of chronic fatigue syndrome”** in which he stated: **“ME/CFS can last for years and is associated with marked impairment. (It) is a terribly destructive illness. The tenacity and ferocity of the fatigue can be extraordinary. As for the symptoms that accompany the fatigue, it is striking that these symptoms are experienced not just occasionally but are present virtually all the time. In our experience, 80% of patients with ME/CFS have an exceptional post-exertional malaise. (Physical examination findings) include abnormal Romberg test (and) hepatomegaly (and) splenomegaly. Anyone who has cared for patients with**

*ME/CFS will recognize that (the) description of the patient with lupus eloquently describes many patients with ME/CFS as well*" (In: Chronic Fatigue Syndrome. John Wiley & Sons, Chichester. Ciba Foundation Symposium 173:43-61).

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

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

That same year, UK researchers Geoffrey Clements et al reported that: "*Enteroviral sequences were found in significantly more ME/CFS patients than in the two comparison groups. The presence of the enteroviral sequences in a significant number of patients points to some role in ME/CFS. A variety of immunological disturbances have been reported for ME/CFS patients which may relate in some way to the enteroviral persistence. This study provides evidence for the involvement of enteroviruses in just under half of the patients presenting with ME/CFS and it confirms and extends previous studies using muscle biopsies. **We provide evidence for the presence of viral sequences in serum in over 40% of ME/CFS patients***" (J Med Virol 1995:45:156-161).

In 1997, US researchers studied the quality of life of persons with ME/CFS and found that "*The quality of life is particularly and uniquely disrupted in ME/CFS. All participants stated that ME/CFS had had a profound impact on every aspect of their lives in ways they had never imagined possible*". The researchers found that the impact of ME/CFS on the patients' life was so total and so devastating that participants had difficulty in accepting their illness and its consequences.

Also in 1997, Charles Lapp, Professor of Community Medicine at Duke University, Charlotte, North Carolina, found that a trial allowing ME/CFS patients to reach their maximum oxygen consumption within 8-10 minutes of exercise caused 74% to experience a worsening of fatigue and that none improved. The average relapse lasted 8.82 days. Lapp concluded: "*These findings suggest that, pushed to maximal exertion, patients with ME/CFS may relapse*" (Am J Med 1997:103:83-84).

In 1998, a study of autonomic function by Rowe and Calkins found that "*Virtually all ME/CFS patients (regardless of their haemodynamic response) have their symptoms provoked by standing upright*" (Am J Med 1998:105: (3A):15S – 21S).

Also in 1998, US researchers presented key evidence: "*The results showed that in ME/CFS patients, a lower stroke volume was highly predictive of illness severity: across three different postures, the most severely affected patients were found to have a lower stroke volume and cardiac output compared with those with more moderate illness. These findings suggest a low flow circulatory rate in the most severe cases of ME/CFS; this may indicate a defect in the higher cortical modulation of cardiovascular autonomic control. In the most severely affected, situations may arise where a demand for blood flow to the brain may exceed the supply, with a possibility of ischaemia and a decrement of function*" ("CFS severity is related to reduced stroke volume and diminished blood pressure responses to mental stress" Arnold Peckerman Benjamin Natelson et al. Presented at the Fourth International AACFS Research & Clinical Conference on ME/CFS, Mass. USA).

In 1998, Racciatti et al found that "*(ME)CFS is a severely disabling illness. Regional brain perfusion impairment (mainly hypoperfusion) was found in 83.9% of (ME)CFS patients. This study confirmed previous reports of brain perfusion impairment in (ME)CFS, providing objective evidence of central nervous system dysfunction*". ("Brain SPET in Chronic Fatigue Syndrome": Fourth AACFS International Research & Clinical Conference, Mass: USA).

**The NICE Guideline specifically proscribes such scans to assist in the diagnosis of patients with “CFS/ME”.**

That same year, UK researchers Russell Lane and Leonard Archard published their findings of muscle abnormalities in response to exercise in ME/CFS patients: *“The object of this study was to examine the proportions of types I and II muscle fibres and the degree of muscle fibre atrophy and hypertrophy in patients with ME/CFS in relation to lactate responses to exercise, and to determine to what extent any abnormalities found might be due to inactivity. Muscle fibre histometry in patients with ME/CFS did not show changes expected as a result of inactivity. The authors note that one of these patients had an inflammatory infiltrate, and it would seem that inflammation and class I MHC expression may occur in biopsies from patients with ME/CFS. The authors note that this is of some interest, as they have argued previously that some forms of ME/CFS may follow a previous virally-mediated inflammatory myopathy”*. In general, following exercise, patients with ME/CFS showed more type I muscle fibre predominance and infrequent muscle fibre atrophy, unlike that which would be expected in healthy sedentary people. (JNNP 1998:64:362-367).

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

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

In 2001 an Australian study by Sargent, Scroop, Burnett et al from the Adelaide CFS Research Unit found that ME/CFS patients are not de-conditioned and that “There is no physiological basis for recommending graded exercise programmes” (The Alison Hunter Memorial Foundation ME/CFS Clinical and Scientific Meeting, Sydney, Australia, December 2001).

This was later published (Med. Sci. Sports Exerc: 2002:34:1:51-56) and the authors stated: *“The fatigue is often present at rest and exacerbated by the simplest of physical tasks. The purpose of the present study was to employ ‘gold standard’ maximal exercise testing methodology. Exercise performance is well recognised to be impaired in ME/CFS patients, with a reduced exercise time to exhaustion being a common finding. The present findings indicate that physical deconditioning (is not) a critical factor in the fatigue that (patients) experience. Although the recommendation or imposition of exercise-training programmes may have benefit in terms of social interaction, such programmes could well be based on a false premise if the intention is to improve well-being by correcting the effects of deconditioning”*.

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



Also in 2003, Peckerman and Natelson et al from the US were specific about circulatory problems in ME/CFS: ***“Findings indicative of a problem with circulation have been reported in patients with ME/CFS. (Our) results provide evidence of reduced cardiac output in severe ME/CFS. They suggest that in some patients, blood pressure is maintained at the cost of restricted flow, possibly resulting in a low circulatory state. Thus there may be periods in daily activities when demands for blood flow are not adequately met, compromising metabolic processes in at least some vascular compartments. Several deficiencies capable of affecting cardiac output have been reported in ME/CFS, including lower blood volume, impaired venous regulation, and changes in autonomic, endocrine and cardiac function. The abnormalities causing a reduction in cardiac output in ME/CFS thus may be dispersed over multiple systems. (Further research) should be directed at conditions that may not be overtly expressed in symptoms of ME/CFS, such as under-perfusion in the kidneys and the gut, as the organs in which the initial conservation of cardiac output takes place. The patients with severe ME/CFS had significantly lower stroke volume and cardiac output than the controls and less ill patients. In summary, this study provides indication of reduced cardiac output in some patients with ME/CFS”*** (Am J Med Sci 2003;326:2:55-60).

In 2003, Byron Hyde, medical adviser on ME/CFS to the Canadian Government, pointed out that ***“ME in adults is associated with measurable changes in the central nervous system and autonomic function and injury to the cardiovascular, endocrine and other organs and systems. The patient with the diagnosis of ME/CFS is chronically and potentially seriously ill. These ME/CFS patients require a total investigation and essentially a total body mapping to understand the pathophysiology of their illness and to discover what other physicians may have missed. A patient with ME is a patient whose primary disease is central nervous system change, and this is measurable. The belief that ME/CFS is a psychological illness is the error of our time”***. (The Complexities of Diagnosis. Byron Hyde. In: Handbook of Chronic Fatigue Syndrome Leonard A Jason et al. John Wiley & Sons, Inc. 2003).

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

In the Summer of 2004, Professors Christopher Snell and Mark VanNess from the University of the Pacific (specialists in sports medicine and muscle function who have been involved in ME/CFS research since 1998) published an article in The CFIDS Chronicle in which they wrote: ***“Healthcare professionals often recommend aerobic exercise as a cure-all for the symptoms of ME/CFS without fully understanding the consequences (and) the results can be devastating (and can lead to) symptom exacerbation, post-exertional malaise and even collapse. It is obvious that persons with ME/CFS do not recover well from aerobic activity. This may be because, for them, the activity is not aerobic. The aerobic system depends on a constant supply of oxygen being delivered to active muscles. There is evidence that this process may be impaired in ME/CFS. In the absence of an adequate supply of oxygen, energy production shifts to anaerobic (without oxygen) process, leading to oxygen debt. Oxygen debt equals fatigue and before normalcy can return (that debt) must be repaid. Interest rates on the (oxygen debt) may be significantly high. Exercise therapy for ME/CFS will not work because one size does not fit all”***.

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

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

At this Conference, findings were presented by a Belgian team (Nijs) which provided **evidence of underlying lung damage through intracellular immune dysregulation, with impairment of**

**cardiopulmonary function** – elevated elastase levels could damage lung tissue and impair oxygen diffusion across the alveoli in the lungs, potentially explaining decreased oxygen delivery to tissues that is seen in ME/CFS. (This presentation was singled out as being outstanding).

The “Exercise Workshop” at this same conference highlighted the understanding that people with ME/CFS suffer exercise intolerance and post-exertional malaise unless they stay within prescribed limits, the limit suggested being the anaerobic threshold (AT -- this is the time during exertion that the heart and lungs can no longer provide adequate oxygen to muscles, and muscle metabolism changes from aerobic to anaerobic; it is well known that this change occurs unusually early in people with ME/CFS). If the anaerobic threshold is determined to occur at 4.5 minutes, then the patient is advised to exert no more than 4 to 4.5 minutes before stopping to rest.

(For conference reports, see <http://www.drlapp.net/AACFS%20Meeting%20Summary.htm> by Professor Charles Lapp from the US and Co-Cure NOT, RES: 2<sup>nd</sup> November 2004 by Dr Rosamund Vallings from New Zealand).

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

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

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

In 2006, Belgian researchers Nijs and De Meirleir reported on the observed associations between musculoskeletal pain severity and disability, noting that pain was as important as fatigue to ME/CFS patients: ***“A few years ago, little was known about the nature of chronic musculoskeletal pain in ME/CFS. Research data gathered around the world enables clinicians to understand, at least in part, musculoskeletal pain in ME/CFS patients. Fear of movement (kinesiophobia) is not related to exercise performance in ME/CFS patients. From a pathophysiologic perspective, the evidence of a high prevalence of opportunistic infections is consistent with the numerous reports of deregulated and suppressed immune functioning in ME/CFS patients. Infection triggers the release of the pro-inflammatory cytokine interleukin-1  $\beta$  which is known to play a major role in inducing cyclooxygenase-2 (COX-2) and prostaglandin E2 expression in the central nervous system. Upregulation of COX-2 and prostaglandin E2 sensitises peripheral nerve terminals. Even peripheral infections activate spinal cord glia (both microglia and astrocytes), which in turn enhance the pain response by releasing nitric oxide (NO) and pro-inflammatory cytokines. These communication pathways can explain the wide variety of physiological symptoms seen in ME/CFS. Experimental evidence has shown that ME/CFS patients respond to incremental exercise with a lengthened and accentuated oxidative stress response, explaining muscle pain and post-exertional malaise as typically seen in ME/CFS. In many of the published studies, graded exercise therapy has been adopted as a component of the CBT programme (i.e. graded exercise was used as a way to diminish avoidance behaviour towards physical activity). Unfortunately, the studies examining the effectiveness of GET/CBT in ME/CFS did not use musculoskeletal pain as an outcome measure (and) none of the studies applied the current diagnostic criteria for ME/CFS. From a large treatment audit amongst British ME/CFS patients, it was concluded that approximately 50% stated that GET worsened their condition. Finally, graded exercise therapy does not comply with our current understanding of ME/CFS”***

***exercise physiology. Evidence is now available showing increased oxidative stress in response to (sub)maximal exercise and subsequent increased fatigue and post-exertional malaise*** (Manual Therapy 2006: Aug. 11(3):187-189).

In 2007 a study by Lerner et al found that “***A progressive cardiomyopathy caused by incomplete virus multiplication in ME/CFS patients is present***” (In Vivo 2004:18:4:417-424).

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

In 2008, a collaborative study involving researchers from Belgium, the UK and Australia (published by J Nijs, L Paul and K Wallman as a Special Report in J Rehabil Med 2008:40:241-247) examined the controversy about exercise for patients with ME/CFS. Although published after the production of the NICE Guideline, the paper contains relevant references showing adverse effects of GET that were published before the Guideline (and so were available to the GDG): “***ME/CFS describes a disorder of chronic debilitating fatigue that cannot be explained by any known medical or psychological condition. The Cochrane Collaboration advises practitioners to implement graded exercise therapy for patients with ME/CFS, using cognitive behavioural principles. CBT represents a psychological and physical intervention approach aimed at assisting individuals in re-evaluating concepts related to their illness and in adopting thoughts and behaviours designed to promote recovery*** (the reference for this statement is Chalder, Deale and Wessely et al. Am J Med 1995:98:419-420). ***This approach to GET advises patients to continue exercising at the same level even when they develop symptoms in response to exercise*** (two references are provided for this statement, one being Fulcher KY and White PD, BMJ 1997:314:1647-1652 – this being one of the RCTs based on the Oxford criteria that the GDG relied upon for its recommendation of GET. The other reference was Clark LV and White PD (J Mental Health 2005: 14: 237-252), in which Clark and White state that patients with ME/CFS are de-conditioned, and argue that: “***Patient education is necessary to inform patients of the positive benefit / risk ratio in order to improve acceptance and adherence***”). Nijs et al continue: “***Conversely, there is evidence of immune dysfunction in ME/CFS, and research shows further deregulation of the immune system in response to too-vigorous exercise, leading to an increase in fatigue and post-exertional malaise. It has been shown that even a 30% increase in activity frequently triggers a relapse*** (ref: Black CD, O’Connor, McCully K. Dynamic Medicine 2005:4:3). ***The severe exacerbation of symptoms following exercise, as seen in patients with ME/CFS, is not present in other disorders where fatigue is a predominant symptom. This post-exertional malaise is a primary characteristic evident in up to 95% of people with ME/CFS. It is possible that exercise at ANY intensity that exceeds an ME/CFS patient’s physical capabilities may result in the worsening of symptoms. Early approaches to GET advised patients to continue exercising at the same level when they developed symptoms in response to the exercise. This led to exacerbation of symptoms and adverse feedback from patient and patient charities***”.

This last sentence cites the work of Professor Peter White, so attention is again drawn to the fact that his study of 1997 is one upon which the GDG relied to recommend **incremental aerobic exercise**.

There is an extensive literature from 1956 to date on the significant pathology that has been repeatedly demonstrated in ME/CFS, but not in “CFS/ME”; this can be accessed on the ME Research UK website at <http://www.mereseearch.org.uk/information/researchdbase/index.html> .

It includes evidence of an over-activated immune system but with low NK cell function, and abnormal dysregulation of the 2-5A synthetase / RNase-L pathway (a critical anti-viral pathway and part of the body’s essential natural antiviral defences: in ME/CFS a protein that in healthy controls weighs 80 kDa [kiloDalton] uniquely weighs only 37kDa), these latter two being specific markers of the disease. Elevated levels of RNase-L are associated with reduced maximal oxygen consumption (VO<sub>2</sub>max) and exercise duration in ME/CFS patients. Both abnormal RNase-L activity and low oxygen consumption are observed in most patients with ME/CFS and demonstrate patients’ extremely low tolerance for physical activity. Overseas researchers have found that testing the ratio of the 37kDa and 80kDa enzymes has revealed that a

high ratio is associated with more severe clinical symptoms (such testing is proscribed by the GDG in the NICE Guideline). For detailed references, see “Chronic Fatigue Syndrome: A Biological Approach” edited by Patrick Engelbienne and Kenny De Meirleir; CRC Press: 2002.

Other significant abnormalities have been demonstrated on nuclear imaging such as MRI (looking at brain structure), fMRI (looking at brain function), MRS (looking at the chemistry of the brain), SPECT (looking at bloodflow in the brain) and PET (looking at brain metabolism) scans. It is notable that MRS scans of patients with ME/CFS have revealed free choline, which is indicative of active viral infection in the brain, with damage to the nerve cell membranes (Tomoda A et al. Brain Dev 2002;22:60-64; Puri BK et al. Acta Psychiatrica Scand 2002;106(3):224-226; Chaudhuri A et al. Neuroreport 2003;14:225-228). As noted above, such imaging in ME/CFS patients is proscribed by the GDG.

It has long been shown that in ME/CFS there is dysfunction of the autonomic nervous system (adversely affecting temperature control, respiration; bladder and bowel control; heart rate; blood pressure control, with neurally-mediated hypotension [NMH] and postural orthostatic tachycardia syndrome [POTS] etc). Yet more biomedical abnormalities have been shown to include low levels of cortisol; problems with fluid balance; abnormal thyroid function; muscle abnormalities; impaired oxygen delivery to muscles; cardiac dysfunction, and abnormal EEG profiles.

Unique vascular abnormalities have been demonstrated in ME/CFS, with markers of oxidative stress: oxidative stress is caused by highly reactive molecules known as free radicals circulating in the bloodstream of people with ME/CFS and results in cell injury; research has shown that many patients with ME/CFS could have an inflammatory condition and be in a ‘pro-oxidant’ state; **exercising muscle is a prime contender for excessive free radical generation.**

There is convincing research from Belgium which demonstrates that an intracellular inflammatory response in the white blood cells plays an important role in the pathophysiology of ME/CFS and that **patients’ symptoms reflect a genuine inflammatory response** (Maes M et al. Neuro Endocrinol Lett 2007;28(4) ).

Research from Australia has demonstrated that patients with ME/CFS have a broad and variable spectrum of signs and symptoms, with alterations in standard blood parameters and in urinary excretion profiles. These alterations include a significant decrease in red cell distribution width and increases in mean platelet volume, neutrophil counts, and the neutrophil / lymphocyte ratio. The urinary abnormalities include a reduced rate of amino acid excretion, with significant decreases in asparagine, phenylalanine and succinic acid, as well as increases in 3-methylhistidine and tyrosine. The authors conclude that this data supports the existence of alterations in physiologic homeostasis in ME/CFS patients (“Haematologic and urinary excretion anomalies in patients with chronic fatigue syndrome”. Niblett SH, Dunstan RH, McGregor NR et al. Exp Biol Med 2007;232(8):1041-1049). This group has identified amino acids and their derivatives as indicators of disturbed metabolic pathways which reflect the clinical features of ME/CFS: excreted 3-methylhistidine is an established marker of active breakdown of muscle.

These abnormalities have not been seen in “chronic fatigue” (i.e. in “CFS/ME”).

In summary, the GDG ignored the published evidence (not hypotheses) of the following:

- evidence of disrupted biology at cell membrane level
- evidence of abnormal brain metabolism
- evidence of a reduction in grey matter
- evidence of widespread abnormal cerebral perfusion (hypoperfusion)
- evidence of central nervous system / immune dysfunction
- evidence of central nervous system inflammation and demyelination
- evidence of hypomyelination
- evidence of spatial disorientation
- evidence that ME/CFS is a complex, serious multi-system autoimmune disorder (in Belgium, the disorder has now been placed between MS and lupus)

- evidence of significant neutrophil apoptosis
- evidence that the immune system is chronically activated (eg. the CD4:CD8 ratio may be grossly elevated, as seen in multiple hypersensitivities)
- evidence that NK cell activity is impaired (ie. diminished)
- evidence of hair loss in ME/CFS
- evidence that the vascular biology is abnormal, with disrupted endothelial function
- novel evidence of significantly elevated levels of isoprostanes (a marker for oxidative stress, which in ME/CFS goes up with exercise intolerance)
- evidence of impaired proton removal from muscle during exercise
- **evidence of cardiac insufficiency and that patients are in a form of heart failure**
- evidence of autonomic dysfunction (especially thermo-dysregulation; frequency of micturition with nocturia; haemodynamic instability with labile blood pressure; pooling of blood in the lower limbs; reduced blood volume (with orthostatic tachycardia and orthostatic hypotension)
- evidence of respiratory dysfunction, with reduced lung function in all parameters tested
- evidence of neuroendocrine dysfunction (notably HPA axis dysfunction)
- **evidence of recovery rates for oxygen saturation that are 60% lower than those in normal controls**
- evidence that the average maximal oxygen uptake was only 15.2 ml/kg/min, whilst for controls it was 66.6 ml/kg/min
- **conclusive evidence of delayed recovery of muscles after exercise**, with ME/CFS patients reaching exhaustion more rapidly than controls, with this failure to recover being more pronounced 24 hours after exercise (note: there is no evidence of de-conditioning)
- evidence of mitochondrial metabolic dysfunction
- evidence of inability to sustain muscle power
- evidence of greatly increased REE (resting energy expenditure)
- evidence of enteroviral particles in muscle biopsies
- **evidence of a sensitive marker of muscle inflammation (inflamed tissues should not be exercised)**
- evidence of on-going infection
- evidence that the size of the adrenal glands is reduced by up to 50% (with reduced cortisol levels)
- evidence that up to 92% of ME/CFS patients also have irritable bowel syndrome (80% of the immune system is located in the gut)
- evidence of abnormal gene expression (at least 35 abnormal genes -- acquired, not hereditary), specifically those that are important in energy metabolism; **there are more abnormal genes in ME/CFS than there are in cancer**
- evidence of profound cognitive impairment (worse than occurs in AIDS dementia)
- evidence of adverse reactions to medicinal drugs, especially those acting on the central nervous system, such as anaesthetics
- evidence that symptoms fluctuate from day to day and even from hour to hour
- there is no evidence that ME/CFS is a psychiatric or behavioural disorder.

#### Abnormal signs in ME/CFS

The NICE Guideline states that there are no abnormal signs in “CFS/ME”. This conflicts with the fact that international research has shown that in ME/CFS there are well-documented abnormal signs, for example:

- labile blood pressure (this is a cardinal sign)
- nystagmus and vestibular disturbance
- sluggish visual accommodation
- fasciculation
- hand tremor
- neuromuscular incoordination
- cogwheel movement of the leg on testing

- muscular weakness
- marked facial pallor
- postural orthostatic tachycardia syndrome (POTS)
- positive Romberg
- abnormal tandem or augmented tandem stance
- abnormal gait
- vascular signs such as demarcation that can cross dermatomes
- evidence of Raynaud's syndrome and vasculitis
- mouth ulcers
- hair loss
- flattened or even inverted T-waves on 24 hour Holter monitoring
- racing heart rate even at rest
- cold and discoloured extremities
- easy bruising
- singular reduction in lung function tests
- abnormal glucose tolerance curves
- enlarged liver (not usually looked for by psychiatrists)

These abnormalities have nothing to do with "illness beliefs". Aberrant illness beliefs have nothing to do with ME/CFS.

In producing its Guideline, the GDG failed to consider any of this evidence that contra-indicates incremental aerobic exercise.

**Despite this failure, NICE still claimed that its Guideline represents the best available evidence: "This guideline offers best practice advice on the care of people with CFS/ME" (52 page version, page 6). Such a statement is indefensible and unsustainable.**

#### **Documented medical concern about GET for patients with ME/CFS that the GDG ignored**

As long ago as 1989, the charity Action for ME published a warning about graded exercise programmes in its magazine Interaction No.2: *"There has been much talk in the medical literature about 'Graded Exercise' or 'Rehabilitation' programmes for ME sufferers. In spite of all the evidence to the contrary, some doctors have suggested that there is nothing wrong with the muscles of ME sufferers, and there are at least two programmes under way, at the National Hospital for Nervous Diseases in London, and at the Royal Liverpool Hospital, which encourage ME sufferers to gradually increase the amount of exercise they are doing. There is no evidence to suggest that pushing oneself to exercise beyond one's limit can do any good. We have had reports from Liverpool and London of sufferers who have been severely relapsed by 'graded exercise programmes' "*

Seventeen years after this warning, Dr Derek Pheby, Project Co-ordinator at The National ME Observatory, was obliged to point out to NICE that: *"CBT and GET should not be regarded as the first choice of treatment or as providing a cure"* (CG53 website).

A member of the Association of British Neurologists pointed out to NICE that: *"The Guideline should not re-define CFS/ME to fit in CBT and GET as the recommended treatment options. Listen to patients"* (CG53 website).

NICE claims to have been guided by the CMO's Working Group Report of January 2002, but that Report records concern about GET: *"Existing concerns include the view that patients have a primary disease process that is not responsive to or could progress with graded exercise. Substantial concerns exist about the potential for harm. No other treatment received such negative feedback"* (4.4.2.1:46-47). Referring to the first York Systematic Review of the alleged efficacy of CBT/GET (JAMA 2001), the CMO's Working

Group Report is unambiguous: *“the data clearly indicate that the York Review results do not reflect the full spectrum of patients’ experience”* (Annex 3, section 3).

The Canadian Guidelines are unequivocal: graded exercise showed the highest negative rating of all management interventions: *“The question arises whether a formal CBT or GET programme adds anything to what is available in the ordinary medical setting. A well-informed physician helps (the patient) achieve optimal exercise and activity levels within their limits in a common-sense, non-ideological manner which is not tied to deadlines or other hidden agenda”* (“ME/CFS: Clinical Working Case Definition, Diagnosis and Treatment Protocols”). Bruce M Carruthers, Kenny L De Meirleir, Nancy G Klimas et al. JCFSS 2003;11:1:7-115).

Dr Derek Enlander MD (a former virologist who specialises in ME/CFS, previously Assistant Professor at Columbia University and then Associate Director of Nuclear Medicine at New York University; currently Physician-in-Waiting to the Royal Family and to members of HM Government when they visit New York) is on record about aerobic exercise for patients with ME/CFS: *“I do not want my patients in an aerobic class. I feel this causes considerable damage to ME/CFS patients”* (“Update on the Treatment of Chronic Fatigue Syndrome and Fibromyalgia” 8<sup>th</sup> November 2006).

Moreover, the CDC “CFS Toolkit” released at the beginning of November 2006 is equally clear: ***“This kind of exercise (aerobic) can precipitate a full-scale relapse that lasts for weeks or months”***. The Toolkit section on “Managing Activity” is explicit: *“Advising patients who have (ME/CFS) to engage in aerobic exercise can be detrimental. Most patients cannot tolerate exercise routines aimed at optimising aerobic capacity. Instead of helping patients, such exercise can cause post-exertional malaise, a hallmark of ME/CFS that is defined as exacerbation of fatigue and other symptoms following physical or mental exertion. Even worse, this kind of exercise can precipitate a full-scale relapse that lasts for days or weeks”* (<http://www.cdc.gov/cfs/toolkit.htm>).

Four US experts in ME/CFS have gone on record about the British approach to CBT:

*“One of the most controversial treatments for ME/CFS is cognitive behavioural therapy. Some patients are fiercely opposed to it because they believe it suggests that if they’d just change their behaviour or their attitudes about the illness, they would get better. This opposition has been strengthened by the British approach to CBT”*.

***“I don’t take the British point of view that CBT is the one thing you can do to effectively treat ME/CFS’ says (Professor) Klimas. Dr Lapp agrees. ‘In my opinion CBT is widely but unfairly maligned because of the British approach, which presumes that ME/CFS has no organic basis and is therefore contradictory to current science. This type of CBT assumes somatic symptoms are perpetuated by errant illness beliefs and maladaptive coping’. Dr Bell (says) ‘It won’t suddenly make patients better’. Dr Peterson says he’s ‘not convinced of the efficacy of CBT’ ”***

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

This concern is un-remitting: eight years ago (in June 2000) the Medical Adviser to the ME Association wrote in the charity’s Newsletter “Perspectives”: ***“The ME Association receives far more complaints about graded exercise regimes than any other management issues. Consequently, we are now informing our members that they should consider taking legal action against the health professionals concerned when an inappropriate ‘exercise prescription’ causes a relapse”***.

The following year, the Medical Adviser to the ME Association wrote in the Medical and Welfare Bulletin (published by the ME Association, Spring 2001) that he continued to receive more adverse reports about graded exercise than any other form of intervention and that there is clear confirmation that many people with ME/CFS are suffering relapses through such programmes.

The Guideline itself carries repeated warnings about GET:

*“A general exercise programme can cause significant symptom exacerbation”* (Full Guideline: 6.3.1.2, page 191).

*“Healthcare professionals delivering a GET programme should do so with a degree of caution, recognising that for many patients with CFS/ME, GET can cause an increase in symptoms which can be distressing”* (Full Guideline: 6.3.1.2, page 191).

Even more disturbing are the responses made by the GDG to stakeholders’ submitted concerns; these were not made public until 2<sup>nd</sup> October 2007, which was after the Guideline was published on 22<sup>nd</sup> August 2007. In relation to the potential dangers of GET, the same GDG response occurs no less than ten times (CFS/ME Stakeholders’ Comments and GDG Responses (575 pages): pages 16, 38, 66, 156, 229, 235, 412, 490, 508 and 571). That response says: *“The term GET has been applied to a variety of programmes. As indicated in the patient evidence, some of these have unfortunately had deleterious, not to say disastrous, effects on patients”* (<http://www.nice.org.uk/guidance/index.jsp?action=folder&o=36179> ).

It is notable that the Guideline continually emphasises that GET should be carried out cautiously and should be tailored to individual needs, yet this recommendation does not relate to the GDG’s stated evidence-base on which they profess to have relied: for example, that evidence-base recommends: *“If patients complained of increased fatigue, they were advised to continue at the same level of exercise”* (Fulcher and White, BMJ 1997:314:1647-1652).

Since such advice is not what the Guideline recommends, it is unclear upon what RCT evidence-base the GDG relied for its own version of GET.

### **The implementation of the type of GET that the GDG recommends**

The Guideline stipulates that GET programmes must be tailored to the individual, but does not adequately address the logistics of administering such individual programmes. The reality is that mild to moderately affected patients are referred to the CFS Centres set up by the Government specifically to deliver CBT/GET. A substantial body of evidence has been collated by Paul Davis of Campaigning for Research into ME (RiME: [www.erythos.com/RiME](http://www.erythos.com/RiME) ) documenting the dismay, dissatisfaction and deep concern about the type of therapy in force at these Centres. This concern has been presented at numerous All Party Parliamentary Group on ME meetings held at the Palace of Westminster. The evidence is that these CFS clinics make no distinction between those with ME/CFS and those with chronic “fatigue”, and that patients with ME/CFS are bullied and coerced into taking part in aerobic exercise that is beyond their capabilities, with sufferers being told by therapists that they have a ‘fear of activity’ and ‘motivation problems’.

Advertisements for therapists at some of the thirteen NHS CFS Centres make disturbing reading:

- the Liverpool “CFS” Clinical Network Co-ordinating Centre’s advertisement for therapists informed applicants that “CFS” patients have perpetuating illness behaviour; that they experience barriers to understanding; that there can be significant barriers to accepting the changes needed in behaviour, which have to be overcome in therapy in order to facilitate a successful outcome; that the **Fatigue Therapist** will be required to modify patients’ predisposing personality style and provide motivation to patients with CFS; that some clients may be resistant to working in a psychological framework and that there may be verbal aggression. *“ Individual treatment sessions are up to two hours long and twice weekly group sessions are three hours in length”*. (Chronic Fatigue Treatment Service: Ref: 2570. Closing date: 31<sup>st</sup> January 2005). **The Clinical Champion at this Centre is Dr Fred Nye, a member of the GDG**
- the job description for the CFS Service at Sutton Hospital said: *“The position is for a clinical psychologist who will work as part of a multidisciplinary team for people with persistent fatigue and for whom medical intervention is no longer appropriate. Patients referred to the service*



*may be hostile to the rationale for adopting a cognitive-behavioural approach to the management of their fatigue” (Co-Cure ACT: 13<sup>th</sup> February 2005).*

In a Midlands CFS Centre, the fact that ME/CFS is not being treated as a distinct disorder but is being subsumed under fatiguing illnesses means that a broad-brush approach is being taken. The evidence from patients is that this is happening nationally.

No matter what the Guideline says about the need for individually tailored programmes, this is not what is happening on the ground.

A person with even mild or moderate ME/CFS could not manage a two-hour CBT session, let alone an exercise programme, and those who are severely affected could not manage 30-minute telephone or computer sessions (even supposing that all such patients possess and can use a computer, assuming that the Government is going to pay for those who do not have a computer to be provided with one and be taught how to use it).

The reality is that the individual programmes of GET that the Guideline recommends cannot be delivered because the logistics are impossible, even though the Government has spent £173 million to train therapists throughout England (<http://news.bbc.co.uk/1/hi/health/7486132.stm>), but nothing else is offered to people with ME/CFS.

### **There is no cure for ME/CFS**

The Guideline repeatedly refers to CBT and GET as “treatment”; this is misleading, because “treatment” implies a potential cure. There is no treatment for ME/CFS and CBT/GET is but a management regime.

There is no cure for ME/CFS (CMO’s Working Group Report: January 2002: 4.4.2.2:48). For certain influential psychiatrists to state that full recovery is possible with CBT/GET, as Professor Michael Sharpe did (“*There is evidence that psychiatric treatment can be curative*”. BMB 1991:47:4:989-1005) and as Professor Peter White has done (“*Significant improvement is probable and a full recovery is possible*”. Psychother Psychosom 2007:76(3):171-176) and to infer that patients can recover from ME/CFS if they would only follow NICE’s recommended regime of CBT/GET offers false hope: the recovery statistics simply do not support such a belief.

According to US statistics provided in August 2001 by the Centres for Disease Control (CDC) CFS Programme Update, only 4% of patients had full remission (not recovery) at 24 months. The ME Association Medical Adviser pointed out in 2007 that “*Several research studies looking at prognosis have been published. Results from these studies indicate that ME/CFS often becomes a chronic and very disabling illness, with complete recovery only occurring in a small minority of cases. A recent Systematic Review of 14 studies found a median recovery rate of 7%*” (“ME/CFS/PVFS: An exploration of the key clinical issues prepared for health professionals”. Dr Charles Shepherd & Dr Abhijit Chaudhuri. Published by The ME Association).

For the GDG to offer such people only a management regime that is designed to alter their (correct) perception that they are seriously ill, and to infer that incremental aerobic exercise will result in significant improvement is reprehensible.

### **CBT and GET are already known not to be effective**

It should not be overlooked that after a course of CBT/GET, there is no objective evidence of improvement (only alleged subjective evidence) and that the transient gains may be illusory (“Interventions for the Treatment and Management of Chronic Fatigue Syndrome -- A Systematic Review”. Whiting P, Bagnall A-M et al; JAMA 2001:286:1360-1368).

Although the GDG places such reliance upon so few RCTs, the Medical Director of the ME Association pointed out in the eBMJ about one of the RCTs upon which the GDG relied ("Is the analysis truly objective?" 1<sup>st</sup> March 2000): "*In one of those trials (Wearden et al. Br J Psychiatry 1998:172:485-490) graded exercise produced only a small amount of improvement, with no significant changes in functional status, and the claim that such programmes can produce substantial improvement in measures of fatigue and physical functioning is incorrect*".

A fundamental question remains unaddressed by the GDG: what sort of exercise programme can safely be used in a disorder that, by its nature, cannot benefit from exercise, and how is a base-line to be determined given that the very features of the disorder include pronounced variability of symptoms from day to day and even from hour to hour?

The Guideline concedes that the best way of measuring outcome in research studies on "CFS/ME" is unknown: "*It is not known how best to measure improvement scientifically for people with CFS/ME and how much of an improvement is significant*" (Full Guideline, page 61). The RCTs of GET do not use measurable (i.e. objective) measures of physical improvement.

Science is all about replicable and consistently accurate measurement: you cannot measure if you do not know how to measure, and without a solid base-line standard for meaningful comparison. You certainly cannot assess a disease by calling it a quite different disease and then recommend a blanket approach to management, but this is exactly what has occurred in CG53.

In her Testimony in the Guideline (3.3.3), Tanya Harrison, a patient representative, is clear: "*I was given a diagnosis of ME, however I recognise that the guideline does not differentiate between ME and CFS*". This suggests that she was being pressurised to support the use of the term "CFS/ME", a paradigm that does not actually exist.

The Cochrane Collaboration Review of 2004 (Issue 2) on Exercise Therapy for CFS by Edmonds et al categorises "CFS/ME" under the Cochrane Depression, Anxiety and Neurosis Group Editorial Group referred to above. As mentioned above, that Editorial Group includes Professor Simon Wessely.

Cochrane Collaboration Reviews are regarded by the Establishment as the gold-standard of meta-analyses of the efficacy of interventions.

In the Cochrane Review of 2004, there are five RCTs of GET that met the criteria for inclusion in a Cochrane Review. Those studies are essentially the same ones as in the York Review of 2005 upon which the GDG relied, the only difference being that the York Review of 2005 used a 2004 follow-up study by Powell et al whereas the Cochrane Review included the original study of 2001 by Powell et al.

Three RCTs (Appleby et al 1995; Fulcher et al 1997; Powell et al 2001) used the Oxford criteria so the results are not generalisable to patients with ME/CFS and two RCTs (Wallman et al 2004 and Moss-Morris et al 2005) used the CDC 1994 criteria. **Initially both the latter had positive subjective results (i.e. decreased perceived fatigue), but after 24 weeks there were no benefits at all.** Most research ignored symptoms other than fatigue and general well-being. None of these RCTs measured the effectiveness of GET on symptoms such as sore throat, swollen glands, dizziness, bowel problems, cardiovascular symptoms etc. **None of the RCTs led to measurable changes in exercise capacity.**

The Cochrane Review Issue 2 states: "*Based on the five included studies, this systematic review concludes that exercise therapy is a promising treatment for CFS. However, studies of higher quality are needed that involve different patient groups and that measure additional outcomes such as adverse effects (and) quality of life over longer periods of time*".

Issue 3 of the same review states: "*It is disappointing that only nine randomised studies of exercise therapy for CFS were found of which five were included, with a total of 336 participants. Only 118 participants contributed to the analysis at 6 months. The limited evidence base limits the precision of the results*".

This should be compared with what Bagnall et al state in their 2005 York Review that was specifically compiled to support the NICE Guideline: ***“The effects of GET were investigated in five fairly large RCTs of patients with CFS, all of which found significant improvement in the intervention”*** (page 53 of 487).

There is clearly a discrepancy about the same evidence-base between the Cochrane Review and the York Review that was produced to support the NICE Guideline, which lends support to the possibility that in their 2005 Review, Bagnall et al were indeed subjected to covert external influence to present the interventions that were to be recommended by NICE in a more favourable light than was warranted, an issue first raised by Hooper and Reid in the report referred to above.

It is notable that Bagnall et al excluded from the York 2005 Review that was done specifically to support the NICE Guideline a major multi-centre study of exercise therapy for CFS/ME mentioned in the Cochrane Review (Guarino P et al. *Controlled Clinical Trials* 2001;22 (3):310-332) that did not find an increase in post-exercise function. That study of 951 patients (CDC 1994 criteria) concluded that the results were less robust than expected and it was noted that complete recovery was never recorded. There was no objective improvement on the exercise test, which was the only objective measure used. The researchers measured work hours pre- and post-exercise, and there was no increase: the number of work hours actually decreased.

Another study of exercise capacity measures in 116 CFS/ME patients fulfilling the CFS 1994 CDC criteria (Pardaens K et al. *Clin Rehabil* January 2006;20:56-66) -- with emphasis on adaptive lifestyle changes -- found only modest changes. The conclusion was curious: ***“Increase in exercise capacity measures is not a necessary condition for reported improvements”***.

That patients do not in fact benefit from these interventions is already a matter of record, being the published views of the keenest proponents themselves:

- CBT and GET are only ***“modestly effective”***. ***“Even though these interventions appear effective, the evidence is based on a small number of studies and neither approach is remotely curative”***. ***“These interventions are not the answer to CFS”*** (Editorial: Simon Wessely *JAMA* 19<sup>th</sup> September 2001;286:11)
- ***“It should be kept in mind that evidence from randomised controlled trials bears no guarantee for treatment success in routine practice. In fact, many CFS patients, in specialised treatment centres and the wider world, do not benefit from these interventions”*** (Huibers and Wessely. *Psychological Medicine* 2006;36:(7):895-900).

This is unequivocal, and would seem to destroy the evidence-base upon which the GDG relied for its management recommendations.

Of cardinal importance is the fact that the alleged evidence-base upon which the GDG relied (in the Systematic Reviews of the literature carried out by the CRD at York) was flawed, as acknowledged by the review team itself: ***“We cannot control the fact that some of the studies are now old, they are mainly UK based and may have methodological flaws. Our Review did not exclude any trials according to their validity. We agree that by itself, the RCT (random controlled trial) / controlled trial evidence base is not an adequate foundation of definitive guidelines”*** (NICE CG53 website).

### **Interventions used by international experts (most of which are proscribed by the GDG for NHS patients)**

The Guideline limits itself to CBT and GET, but experienced clinicians are willing to try various treatment protocols that have been shown to be helpful. These include:

Adrenal support (essential, as cortisol levels have been shown to be extremely low)  
Anti-microbials

Anti-virals (eg. valgancyclovir)  
 Autonomic system-directed medication  
 Cell metabolism support  
 Central nervous system-directed medication  
 Dietary modulation  
 Immunomodulatory drugs  
 Nutritional support (correction of micronutrient imbalances)  
 Mineral supplementation (correction of trace element deficiencies)  
 Pain control  
 Sleep modulation  
 Thyroid support  
 Vitamin supplementation (especially Vitamin D).

### **Conclusion**

**This Guideline seems to be a clear example of the deliberate construction of “policy-based evidence” and not “evidence-based policy”.**

Following publication of their 1991 Oxford criteria, in 1994 two UK psychiatrists who developed those criteria (Wessely and Sharpe) succeeded in including states of “fatigue” in the US CDC Guidelines on “CFS”: *“The exclusion of persons (with psychiatric disorders) would substantially hinder efforts to clarify the role that psychiatric disorders have in fatiguing illness”* (Fukuda et al. Ann Intern Med 1994;121:12:953-959).

This determination of the advisers to the GDG to include all states of “unexplained chronic fatigue” within a single somatoform disorder (“CFS/ME”) was re-confirmed by a member of the GDG. In December 2007 Dr Fred Nye from the Liverpool CFS Centre (whose job advertisement for fatigue therapists was referred to above) went on record confirming that the GDG members had been told that (i) they must avoid the question of aetiology (ii) they should not put “CFS” into any nosological context (iii) they had to play down the well-known association of “CFS” with other poorly understood disorders and (iv) they had to adopt an “inclusive approach”, even though a wide definition risked ‘medicalising’ people who are merely tired. Nye also confirmed that the “consensus” method that was introduced specifically for this particular Guideline *“can conceal what is in effect a voting system”* amongst GDG members (Journal of Infection 2007;55:6:567-571).

Such a watering-down of the key issues that pertain in ME/CFS has been disastrous. It is astonishing how the personal beliefs of a small group of psychiatrists have come to exert such wide-ranging influence in the UK and how their own views (and those whom they advise) remain uninfluenced by the biomedical evidence that shows their beliefs to be seriously misinformed.

In 1994, the charity Westcare (now merged with Action for ME) published The National Task Force Report on CFS/PVFS/ME. This Report was co-funded by The Department of Health. Members of the Task Force included medical specialists in molecular pathology, immunology, neurology, paediatrics, pharmacology and therapeutics, cancer epidemiology and general practice, as well as a consultant physician specialising in ME/CFS. It concluded that ME/CFS remained poorly understood: *“Progress in understanding is hampered by the use by researchers of heterogeneous study groups, the use of study groups which have been selected using different definitions, the lack of standardised laboratory tests (and) the invalid comparison of contradictory research findings stemming from the above”*. The Report stated unambiguously that there is not just one all-embracing chronic fatigue syndrome.

In 1997, a leading US researcher wrote about the *“unfortunate biases”* surrounding ME/CFS: *“Many physicians minimised the seriousness of this disorder and interpreted the syndrome as being equivalent to a psychiatric disorder. These attitudes had negative consequences. It is crucial for ME/CFS research to move beyond fuzzy recapitulation of the neurasthenia concept and to differentiate ME/CFS from other disorders”* (Jason L et al. American Psychologist 1997;52:9:973-983).

Ten years later psychiatrist Dr Eleanor Stein from Canada repeated Jason's message in her keynote lecture at the ME Research UK international conference in May 2007 at the University of Edinburgh: "*We have to sub-group: if we lump everybody together, we will never learn anything, and in twenty years we will still be in the same fuzzy mess*".

Disturbingly, in his letter to the Journal of Infection referred to above, Nye made two particular statements that reveal the flaws of the whole Guideline.

The first was: "*CFS/ME was particularly challenging because ideologically driven controversies about its nature and treatment have been exacerbated by a dearth of good scientific information*". That "ideologically driven controversies about its nature and treatment" exist is the very reason that the Guideline is so flawed. That there is "*a dearth of good scientific information*" is easily shown to be untrue, but it demonstrates the remarkable failure of at least one member of the GDG to be aware of over 4,000 peer-reviewed published papers, textbooks and conference reports about the disorder to which he claims to be referring.

The GDG members are described as "experts" in "CFS/ME". Experts attend international research conferences and are acquainted with the research evidence (known as the grey literature) and the literature about the disorder in which they profess to be experts, but this was not the case with the membership of this particular GDG, as the Medical Adviser to the ME Association noted: "*We find it hard to imagine another situation where a group of people, many of whom have little or no direct experience in the clinical care of an illness they are advising on, have produced such a poor quality guideline*" (MEA Response to the draft Guideline, <http://www.meassociation.org.uk/content/view/243/70/> ).

Nye's second revealing statement was: "*We may have to accept that where the diagnosis and treatment of CFS are concerned, a significant body of opinion will remain opposed to the evidence-based approach adopted by the NHS*". In Nye's view, conclusions based on "opinion" can be disregarded, and only conclusions that are based on "*a serious review of the evidence*" should be heeded. At a stroke, therefore, Nye removes from consideration the evidence of expert patients, which is contrary to both government policy and to the AGREE Instrument to which NICE Guidelines are obliged to adhere (which give equal weighting to patients' experience). The latter part of Nye's sentence does not withstand scrutiny, since the Guideline has been shown not to have been "evidence-based" by virtue of the fact that the few RCT's upon which the GDG relied were seriously flawed.

Given the specific remit of the GDG, and given the vast amount of relevant evidence that the GDG ignored in favour of recommending a psychosocial (behavioural) intervention for people with "CFS/ME", there can be no credible doubt that the GDG failed in all aspects of that remit and that the present Guideline is deeply flawed in relation to the recommended management regime and should therefore be withdrawn.

Almost all the UK major ME/CFS charities have rejected the Guideline on "CFS/ME" as unfit for purpose.

A new Guideline is required, prepared by a different, more balanced and representative GDG, whose advisers are not involved with the medical insurance industry. As the Gibson Report of November 2006 (the Report of a Parliamentary Group) made plain: "*There have been numerous cases where advisors (on ME/CFS) have also had consultancy roles in medical insurance companies. Given the vested interest private medical insurance companies have in ensuring CFS/ME remains classified as a psychological illness, there is blatant conflict of interest here. The Group finds this to be an area for serious concern and recommends a full investigation by the appropriate standards body*". One member of the GDG, Dr William Hamilton, has been Chief Executive of a major medical insurance company for 15 years. Almost two years later, nothing whatever has been done to curtail this blatant conflict of interest and it continues unabated.

The conclusions of the Gibson Report are concise:

- The Canadian Criteria are "*a useful contribution in defining CFS/ME*"
- "*The opposing opinions about the nature of the disease are very problematic*"

- The Gibson Report refers to “ *The inability of some in the medical profession to separate (other disorders) from genuine ME/CFS patients* ”
- “ *In the UK, precedence has been given to psychological definitions* ”.

A new GDG should be required to consider the totality of the existing evidence-base on ME/CFS and to heed the many calls for a recommendation that the direction of future research should focus on the biomedical aspects of the disorder and thus towards a diagnostic test (thereby separating ME/CFS from “chronic fatigue”).

A new GDG should be required to be mindful of the pressing need for appropriate (as distinct from basic) laboratory and neuro-imaging investigations as occurs in other countries.

In addition, a new Guideline should emphasise more robustly than in CG53 the need for clinicians to support patients needing help with activities of daily living (i.e. homecare support from Social Services for those who are eligible) and help with State benefit applications, which are a source of considerable distress to people with ME/CFS, especially the threats of re-assessment every three months and of having such benefits withdrawn unless and until the applicant has undergone a course of CBT/GET. The Guideline should acknowledge that many patients with ME/CFS are simply too sick to be forced to attend psychiatric units and to participate in a “rehabilitation programme” that involves exercising, yet if they fail to do so, they are deemed not to want to get better and their State benefits are withdrawn.

There are many such known cases, including those in which ME/CFS patients have been threatened with being sectioned under the Mental Health Act unless they comply with psychotherapy. Some indeed have been forcibly sectioned despite the fact that they are not mentally ill. Sophia Mirza was forcibly sectioned against her will even though she was not mentally ill but was suffering from severe ME/CFS. Soon afterwards she died from ME/CFS at the age of 32. Her autopsy report revealed severe inflammation affecting the dorsal root ganglia, affecting 75% of her spinal cord. At the inquest, one of the pathologists stated: “*ME describes inflammation of the spinal cord and muscles. My work supports the inflammation theory*” (<http://www.meactionuk.org.uk/Criona.htm> ).

In 1994, “GP” magazine carried an article called “GPs despise the ME generation” (April 1994:46). Little has changed since 1994. The statistics are that 50% of GPs still refuse to believe that ME/CFS exists other than as a behavioural disorder and consequently too many GPs and NHS Consultants refuse to provide vital care and support for those with ME/CFS.

A new Guideline should make it clear that NHS clinicians no longer have the option of refusing to support their patients with ME/CFS, particularly in regard to domiciliary visits when requested by the severely affected, and that for GPs to remove those with ME/CFS from their list on the basis that “*this practice does not treat non-diseases*” will incur immediate disciplinary action (such events increased following a poll in which Professor Simon Wessely was involved that was run by the BMJ in April 2002 which found ME to be a “non-disease” that should be left medically untreated, along with freckles and big ears).

A new Guideline should also make it clear that for ME/CFS to be described by an NHS consultant psychiatrist as a “*pseudo-diagnosis*” (Michael Sharpe, *Occup Med* 1997:47:4:217-227), and for ME/CFS to be described by the same psychiatrist as a condition that should “*not be dignified by the presence of what we call disease*” (Michael Sharpe, *Journal of Psychosomatic Research*: 2002:52:6:437-438) and for the same psychiatrist to describe people with ME/CFS as “*the undeserving sick of our society and health service*” (Michael Sharpe, Lecture in October 1999 at Strathclyde University) should also be a disciplinary matter.

The new Guideline should require that for ME/CFS patients to be referred to by clinicians as a “*piece of pond life*” (Dr Tony Copperfield, the pseudonym of a GP in Essex: “*Doctor*” magazine, December 2000), or to be informed that they should be ashamed of themselves, and that they are abusing the NHS, and that ME is “*psychological self-indulgence*” will no longer be tolerated and will result in immediate censure.

The general body of knowledge concerning ME/CFS that is known about by clinicians and researchers working in the field is now so great that it should be considered serious professional misconduct to pretend that it does not exist, or to ignore it as the GDG chose to do.

The new Guideline should also make it clear that substantial evidence exists to show that somatisation, secondary gain, malingering, aberrant illness beliefs, over-vigilance to normal bodily sensations, exercise phobia leading to de-conditioning, bluffing, being work-shy, being suggestible, being too highly-driven and perfectionist, being slothful, doctor-shopping, attention-seeking, having faulty thought processes, lack of motivation, abuse in childhood, inadequate coping strategies, jumping on the bandwagon, adopting the “fad” of ME, matching symptoms to current media scares, refusing to accept the stigma of mental illness, and contagious sociological hysteria – with all of which ME/CFS patients have for 20 years been charged in the UK medical literature – have nothing to do with ME/CFS.