

NOTES re: GET

8th March 2010

Important points re: terminology

Myalgic Encephalomyelitis (ME) has been classified by the World Health Organisation (WHO) as a neurological disorder since 1969. Currently it is listed in the International Classification of Diseases (ICD), chapter 6, under Disorders of Brain at ICD-10 G 93.3. In 1992 the WHO approved the term “chronic fatigue syndrome” (CFS) as a term by which ME may be known. The term CFS is coded only to ME ICD-10 G93.3, hence the term “ME/CFS” is used to denote the disorder.

However, an influential group of psychiatrists known as the Wessely School who work for the medical and permanent health insurance industry refer to ME/CFS as “CFS/ME” but it is not the same specific disorder.

According to them, CFS/ME is a functional somatic (behavioural) syndrome; in their view, the term refers to undifferentiated states of “medically unexplained chronic fatigue” and includes a wide-ranging spectrum of at least 25 states of chronic fatigue or tiredness; crucially, it specifically includes mental and behavioural (ie. somatoform) disorders.

These psychiatrists insist that this heterogeneous group of “fatigued” people must be managed by psychotherapy, the aim of which is to convince patients that they do not suffer from an organic disorder but are simply deconditioned, a state that they assert is curable by cognitive restructuring to disabuse patients of their aberrant illness beliefs (cognitive behavioural therapy or CBT), together with incremental aerobic exercise (graded exercise therapy or GET) to strengthen their flabby muscles.

Of concern is the Wessely School’s insistence that their term “CFS/ME” includes the distinct disease ME. For example, the literature for the Medical Research Council’s PACE Trial of CBT/GET for “CFS/ME” which is being carried out by Wessely School psychiatrists specifically states that “CFS/ME” is the same as ME, even though their “CFS/ME” model excludes most of the well-documented biomedical evidence-base of ME/CFS and ignores the cardinal symptomatology,

focusing only on chronic “fatigue” as a “continuum of on-going tiredness” and on other manifestations of a behavioural disorder, such as “symptom focusing” or “hypervigilance to normal bodily sensations” and the unproven alleged secondary gain from “adopting the sick role”.

They have no interest in what has been described by a leading US Professor of Psychology as “diagnostic accuracy” (Jason L et al. JCFS 1999:5:3-33).

Even though the prestigious US Centres for Disease Control (CDC) accepts that ME/CFS is not the same as “CFS/ME” and its website confirms that: *“The name ME was coined in the 1950s ME is accompanied by neurological and muscular signs and has a case definition distinct from that of CFS(ME)”* (<http://www.cdc.gov/cfs/cme/wb1032/chapter1/overview.html>), the Wessely School does not accept the neurological status or the WHO classification of ME/CFS.

Because ME/CFS is currently classified by the WHO as neurological disorder, the Wessely School insist that it has dual classification in the ICD, once in the neurological section (ICD-10 G93.3) but again in the mental and behavioural section (ICD-10 F48.0).

This incorrect categorisation of “CFS/ME” as a somatoform disorder has been formally repudiated by the WHO: on 22nd 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”*.

Distinguishing between ME/CFS and “CFS/ME” is not merely a matter of semantics; it is a matter of diagnostic accuracy and appropriate management and care of extremely sick people with a complex neuro-immune disorder (ME/CFS) as distinct from patients with chronic “tiredness” or chronic “unwellness”.

It is a matter of record that the Wessely School intends to “eradicate” ME (Eradicating “Myalgic Encephalomyelitis”. Pfizer/Invicta: 4-5 /LINC UP, 15th April 1992, Belfast Castle) by dropping “ME” from “CFS/ME” when expedient (BMJ 2003:326:595-597) and then to reclassify “CFS” as a behavioural disorder under syndromes of chronic “fatigue” under Mental and Behavioural Disorders at ICD-10 F48.0.

Despite the fact that the WHO has confirmed that ME/CFS cannot be subsumed into any other category and that it cannot be considered the same disorder as “unexplained chronic fatigue” or neurasthenia, the Wessely School is not to be moved.

Simon Wessely was instrumental in a Cochrane Review that states: “*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>).

It is widely understood that the Wessely School and its international collaborators intend to ensure that “CFS/ME” will be included in the newly-formed diagnostic category of CSSD (complex somatic symptom disorder) that will appear in the forthcoming revision of the Diagnostic and Statistical Manual for Mental Disorders (DSM-V) that is currently expected to be published in May 2013.

To meet criteria for the new CSSD category (designed to be the “interface” between medicine and psychiatry and specifically to include MUS / MUPS ie. medically unexplained symptoms or medically unexplained physical symptoms, which is how the Wessely School describe “CFS/ME”), criteria A, B and C are necessary:

- A. Somatic symptoms, which must be either multiple somatic symptoms that are distressing, or one severe symptom
- B. Misattribution, excessive concern or preoccupation with symptoms and illness; at least two of the following are required: (1) high level of health-related anxiety; (2) normal bodily symptoms are viewed as threatening or harmful; (3) a tendency to assume the worst about their health (catastrophizing); (4) belief in the medical seriousness of their symptoms despite evidence to the contrary; (5) health concerns assume a central role in their lives

- C. Chronicity: although any one symptom may not be continuously present, the state of being symptomatic is chronic and persistent (at least six months).

Over the last two decades, every one of those criteria has been levelled at people with ME/CFS by the Wessely School; in fact, the proposed criteria for CSSD represent a template for the Wessely School's assumptions and assertions about the nature of "CFS/ME".

The revision of the DSM is considered by many to be an outrage. Over the years, it has been like a runaway train, gathering momentum and newly-created mental disorders at an alarming rate. There is no science involved – not even remotely. It is simply a show of hands and from what is already known about a huge section of the psychiatric community, the more disorders they can claim the better, because it is all about profits, not patients.

International calls for sub-grouping of "CFS"

The international medical and scientific literature is replete with evidence of the need to distinguish between ME/CFS and CFS/ME (ie. chronic "fatigue") and there is now an unmistakable recognition that sound biomedical research has strengthened the need for sub-grouping of "CFS": for many years, international experts have been calling for such sub-grouping (<http://www.meactionuk.org.uk/Subgroups.htm>).

There are many published international concerns about the Wessely School's lack of scientific exactitude, with urgent calls for accuracy in diagnosis, for example:

1. In 1997 US expert Professor Leonard Jason (a psychologist) expressed concern: *"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).
2. In 2006 Professor Mark Demitrack (a psychiatrist) encapsulated the problem that the Wessely School (and those they influence) decline to address. **He noted the entanglement of physical symptoms and behavioural symptoms, and the various studies by certain psychiatrists purporting to show that the likelihood**

of psychiatric disorder increased with the number of physical symptoms. In relation to (ME)CFS, he noted that dismissing it as a somatoform disorder was inappropriate: *“The observation of specific protracted fatigue and the absence of substantial psychiatric comorbidity argues convincingly that this is an inappropriate and overly simplistic way of approaching this puzzling condition.... it does not seem plausible that any single intervention would be helpful in an undifferentiated majority of patients. It therefore may not be surprising that current treatment options for (ME)CFS appear only modestly effective. Non-response, or partial response is the norm, and more than half of all patients fail to receive any benefit from many interventions”.* Demitrack concluded: *“In the face of accumulating evidence, there is an increasing realisation that a unitary disease model for this condition has been a theoretical and practical impediment to real progress towards effective therapeutics for (ME)CFS. Many treatment studies have, unfortunately, neglected to thoroughly consider the significance of patient selection (and) symptom measurement”* (Pharmacogenomics 2006:7(3):521-528).

3. Dr Alan Gurwitt, a US psychiatrist who does not subscribe to the Wessely School’s behavioural model of ME/CFS, repeatedly expresses his dismay and frustration; for example on 23rd January 2003 he noted about the Wessely School:

“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>).

In 2009 Gurwitt’s concern had become tangible:

“Nationally and from around the world, the stories are much the same. People with (ME)CFS, adults or children, suffering from multiple symptoms, with varying degrees of severity, are dismissed and improperly diagnosed or treated.... There is now a wealth of good information available from research and clinical experience. Is skepticism as to the realities of (ME)CFS and FM still so prevalent that there is little or no motivation to learn about these illnesses? Well, sadly, yes....The lack of correct diagnosis, treatment steps not taken, disdainful and dismissive attitudes do hurt people. Are the skepticism and ignorance simply the result of individual physician decisions? Not at all. The CDC and NIH in the USA, the NHS in the UK, medical societies and medical schools, and prestigious journals, no matter what is said, if anything, shout, by means of their silence or lack of effective action, their disinterest and disbelief.... These skeptics predominate in government, medical school and journal hierarchies so they have, in effect, blocked and

can continue to block the research and clinical teaching necessary to change the picture...(There) is a kind of "old boy bias", opinions formed many years ago, passed on by a form of group-think as the proper and prevailing views, untouched, unexamined, unchanged, and driven by an unwillingness to learn about the new research....When is enough ignorance enough? When the evidence is there, but the will to study it is not, and then harm is done out of this ignorance, does that become an ethical issue, rather than a scientific one?" (Co-Cure ACT: 19th August 2009).

4. In 2007, Jason et al pointed out that *"measurement that fails to capture the unique characteristics of these illnesses might inaccurately conclude that only distress and unwellness characterise these illnesses, thus inappropriately supporting a unitary hypothetical construct called functional somatic syndromes"* (JCFS 2007:14(4):85-103), but the Wessely School seems never even to consider the need to capture the unique characteristics of ME/CFS.

Definition of GET

A key issue is how GET is defined: it may encompass anything from gentle stretching exercises to rigidly controlled incremental aerobic exercise.

However, for patients with "CFS/ME", GET is predicated on the assumption that they are deconditioned.

The Medical Research Council's (MRC) current PACE Trial Identifier into the efficacy of CBT/GET for people with "CFS/ME" states that GET *"will be based on the illness model of both deconditioning and exercise avoidance"*; that CBT *"will be based on the illness model of fear avoidance"*, and that GET is to be incrementally increased, leading to aerobic exercise.

Deconditioning is defined as *"loss of physical fitness as the general physiological response to, for example, a prolonged period of inactivity"* (NICE Full Guideline on CFS/ME, CG53, August 2007, page 12).

In their PACE Trial Manual for GET therapists, Bavinton, Clark and White state: *"Physical deconditioning is characterised by reduced muscle strength and aerobic capacity. This has been supported by a number of exercise studies that have shown reduced exercise tolerance in CFS/ME patient compared to controls. Six of these*

studies found that people with CFS/ME were...at least as deconditioned as sedentary healthy controls". This is remarkable, since the authors of this Manual here vitiate their own hypothesis, **because if some people with CFS/ME are only as "deconditioned as sedentary healthy controls", then CFS/ME cannot be the result of deconditioning.**

There is no evidence of deconditioning in ME/CFS; on the contrary there is evidence that there is no deconditioning: as long ago as 2001, Bazelmans et al demonstrated that deconditioning is not a factor in ME/CFS (Psychol Med 2001:31:107-114) and this was confirmed by Sargent et al the following year (Med Sci Sports Exerc 2002:34:1:51-56).

The key issue is that whilst incremental (graded) aerobic exercise (GET) may be of some benefit to those with somatoform disorders, there is abundant evidence that it is contra-indicated in ME/CFS and may indeed be fatal, yet CBT that incorporates GET is the only intervention recommended by UK's National Institute for Health and Clinical Excellence (NICE).

The alleged evidence-base for the efficacy of GET is non-existent

In the systematic review of GET interventions that was published in JAMA in 2001 (Whiting P, Bagnall A-M et al; JAMA 2001:286:1360-1368), attention was drawn to the high drop-out rates in trials of GET; in one of only five RCTs on GET (Wearden et al. Br J Psychiatry 1998:172:485-490) over one third (38%) dropped out of the GET treatment arm of the trial and the systematic review authors commented: *"The highest drop-out rates were in the behavioural interventions....When deciding what treatments should be given to patients, it is important to take adverse effects, especially those that are so severe as to cause patients to discontinue treatment, into consideration"*. There is no objective evidence of efficacy of GET; indeed, the reviewers noted that any transient gains may be illusory.

A review team charged with ascertaining the efficacy and safety of the recommended intervention might have been expected to show more concern about an overall 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%.

In 2000, the Medical Director of the ME Association had already drawn attention to the Wearden et al study ("Is the analysis truly objective?" eBMJ, 1st 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 major multi-centre study of exercise therapy for CFS/ME (Guarino P et al. *Controlled Clinical Trials* 2001;22 (3):310-332) 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.

In the Cochrane Review of 2004, there are five RCTs of GET that met the criteria for inclusion in a Cochrane Review. Of these five studies of GET, three used the Oxford (1991) criteria which, by their own definition, exclude those with a neurological disorder.

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 about exercise therapy for “CFS”: *“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”.*

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.

International medical concern about the Wessely School's interventions (CBT/GET)

There is tectonic division amongst doctors about the correct interventions for ME/CFS; on the one hand, informed clinicians are aware that graded aerobic exercise is contra-indicated (see below), whilst on the other hand, key Wessely School members claim that it is curative and are on record as stating that full recovery is possible: Professor Michael Sharpe has asserted "*There is evidence that psychiatric treatment can be curative*" (BMB 1991;47:4:989-1005) and Professor Peter White has asserted "*recovery from CFS is possible following CBT....Significant improvement following CBT is probable and a full recovery is possible*" (Psychother Psychosom 2007;76(3):171-176). (It must be borne in mind that "*graded activity is normally considered an integral part of CBT for CFS/ME*" -- full NICE Guideline CG53, 2007, page 51).

Many international ME/CFS experts do not agree with the Wessely School's claims of "cure", for example, on 13th September 2008 Professors Nancy Klimas and Mary Ann Fletcher, immunologists from the University of Miami, provided the following Statement about the UK NICE Guideline (in which the Wessely School was so instrumental) and expressed serious doubt about Professor White's claims of "recovery":

"The overall flavour of the Guideline is to lump together all patients with 'medically unexplained fatigue', from relatively mild to profoundly disabling illness and to treat all patients with a standard approach of gradual reconditioning and cognitive behavioural modification. By lumping such a heterogeneous mix of patients...patients with CFS or ME are left with very limited options, and little hope. In addition, this document proscribes immunological and other biologic testing on patients with (ME)CFS in the UK, despite the evidence in the world's medical literature that such testing produces most of the biomedical evidence of serious pathology in these patients. Equally unfortunate is the Guideline Development Group's recommendation for behavioural modification as the single management approach for all 'medically unexplained fatigue'. This month we participated in the International Conference on Fatigue Science in Okinawa, Japan. Dr Peter White of the UK presented his work using behavioural modification and graded exercise. He reported a recovery rate of about 25%, a

figure much higher than seen in US studies in (ME)CFS and, even if possible, simply not hopeful enough to the 75% who fail to recover”.

It is thus imperative that attention is drawn to the significant international concern about the Wessely School’s continued refusal to heed the biomedical evidence that proves them to be wrong about ME/CFS and about their persistent refusal to heed the empirical evidence from thousands of patients that GET in particular makes at least 50% of participants worse, not better.

Although the UK Government is promoting its “Expert Patient” programme as the way forwards in healthcare, evidence provided by patients who have become expert in managing their own condition continues to be ignored.

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). Cooper found that ***“Graded exercise was felt to be the treatment that made more people worse than any other” and that it had actually harmed patients*** (<http://www.afme.org.uk/res/img/resources/Group%20Survey%20Lesley%20Cooper.pdf>).

Also in 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”.***

In Spring 2001, the Medical Advisor to the ME Association wrote in the Medical and Welfare Bulletin 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.

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 UK Chief Medical Officer’s Working Group Report of January 2002 recorded 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).

In the section of the MRC PACE Trial GET Manual for Therapists entitled *“Adverse effects of GET”*, the Manual’s Wessely School authors inform therapists that *“Surveys by patient groups of their members have suggested that GET may be harmful to some people with CFS/ME. It is now believed this finding was due to inappropriately planned or progressed exercise programmes, possibly undertaken independently or under supervision from a person without appropriate experience”*. However, the results of a 2003 AfME Membership Survey (*“Your experiences”*) in relation to GET show that when administered by a physiotherapist, 67% had a negative response and 33% had a positive response and when administered by an occupational therapist, 100% had a negative response and 0% had a positive response (Co-Cure RES, ACT: 5th February 2010), thus demolishing claims that adverse events are the result of inexpertly delivered interventions.

Also in 2003, the Canadian Guidelines were 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”* (Bruce M Carruthers, et al. JCFS 2003:11:1:7-115).

The 25% ME Group for the Severely Affected carried out a further survey in 2004 which found that **93% of respondents found GET to be unhelpful, with 82% reporting that their condition was made worse** (<http://www.25megroup.org/Group%20Leaflets/Group%20reports/March%202004%20Severe%20ME%20Analysis%20Report.doc>).

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

In November 2006 the CDC “CFS Toolkit” was 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>).

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

Even more disturbing are the responses made by the National Institute for Health and Clinical Excellence (NICE) to stakeholders’ submitted concerns about its Guideline (CG53); these were not made public until 2nd October 2007, which was after the Guideline was published on 22nd August 2007. In relation to the potential dangers of GET, the same 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>).

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

In 2009, the Norfolk and Suffolk ME Patient Survey of 225 respondents stated: *“Respondents found the least helpful and most harmful interventions were Graded*

Exercise Therapy and Cognitive Behavioural Therapy" (<http://www.norfolkandsuffolk.me.uk/surveylink.html>).

There is thus an abundance of empirical evidence from ME/CFS patients and charities that GET can result in high rates of adverse effects.

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 in ME/CFS, cardiac output often 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).

The Wessely School pays no heed to international concern about GET, for example:

United States:

"Our reluctance to endorse graded activity arises from our vastly different clinical experience in the US" (Friedberg F, Jason LA. American Psychological Association, Washington, 1998).

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

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).

New Zealand:

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

In 1999, a prominent American researcher, Professor Paul Cheney, 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 (ME)CFS.

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).

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

*the activity is not aerobic. The aerobic system depends on a constant supply of oxygen being delivered to active muscles. There is evidence that this process may be impaired in ME/CFS. In the absence of an adequate supply of oxygen, energy production shifts to anaerobic (without oxygen) process, leading to oxygen debt. Oxygen debt equals fatigue and before normalcy can return (that debt) must be repaid. Interest rates on the (oxygen debt) may be significantly high. **Exercise therapy for ME/CFS will not work because one size does not fit all**".*

A single exercise test is unlikely to reveal any abnormality and serial testing is essential because it is the second test that provides objective evidence of abnormality in ME/CFS patients and of their inability to work. This is clear from the literature, and was unambiguously demonstrated at the 8th International Association of Chronic Fatigue Syndrome (IACFS) Conference held at Fort Lauderdale, Florida, from 10th-14th January 2007. Margaret Ciccolella and Professor Christopher Snell et al from Stockton, CA, demonstrated that patients show extreme abnormalities in a next-day / second session of exercise. They do not recover in 24 hours. In one study, only one patient had recovered to baseline within 48 hours. These changes in serial testing point to a significant and confirmable physical abnormality, verifying the cardinal symptom of post-exertional malaise. This test / retest exercise test is 100% objective and can prove to the insurance companies and agencies of the State that ME/CFS is neither malingering nor faking. In ME/CFS patients, the measurements declined by about 25%, far more than in other significant diseases such as COPD (chronic obstructive pulmonary disease) and even heart failure.

Unique vascular abnormalities have been demonstrated in ME/CFS, with markers of oxidative stress. Oxidative stress is caused by highly reactive molecules known as free radicals circulating in the bloodstream and results in cell injury. Oxidative stress levels are significantly raised in ME/CFS and are associated with clinical symptoms. (Kennedy G, Spence VA, McLaren M, Hill A, Underwood C, Belch JFF. Free Radical Bio Med. 2005;39:584-589).

Exercising muscle is a prime contender for excessive free radical generation
(Niess AM, Simon P.
Front Biosci. 2007 Sep 1;12:4826-38).

Research has shown that many patients with ME/CFS may have an inflammatory condition and be in a 'pro-oxidant' state (Klimas NG, Koneru AO. Curr Rheumatol Rep. 2007;9(6):482-7).

According to Professor Nancy Klimas, ME/CFS can be as severe as congestive heart failure **and the most important symptom of all is post-exertional relapse** (presentation at the ME Research UK International Conference held in Cambridge in May 2008).

Documented pathology seen in ME/CFS that specifically contra-indicates the use of GET

There is an extensive literature **from 1956 to date** on the significant pathology that has been repeatedly demonstrated in ME/CFS, but not in “CFS/ME” or “chronic fatigue”; this can be accessed on the ME Research UK website at <http://www.mereseearch.org.uk/information/researchdbase/index.html> and also at http://www.meactionuk.org.uk/Organic_evidence_for_Gibson.htm . In particular, there is a significant literature on mitochondrial defects (structural and functional) in ME/CFS which the Wessely School continues to ignore.

Some illustrations include the following:

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

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

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

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

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

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

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

In 1990, a UK researcher pointed out the folly of CBT/GET: “*It has been suggested that a new approach to the treatment of patients with postviral fatigue syndrome would be the adoption of a cognitive behavioural model*” (Wessely S, David A et al. JRCGP 1989:39:26-29). *Those who are chronically ill have recognised the folly of the approach and, far from being maladaptive, their behaviour shows that they have insight into their illness*” (D O Ho-Yen JRCGP 1990:40:37-39).

Also in 1990, the BMJ published an important study: “*Patients with the chronic fatigue syndrome have reduced aerobic work capacity compared with normal subjects. We found that patients with the chronic fatigue syndrome have a lower exercise tolerance than normal subjects. Previous studies have shown*

biochemical and structural abnormalities of muscle in patients with the chronic fatigue syndrome" (Aerobic work capacity in patients with chronic fatigue syndrome. MS Riley DR McClusky et al BMJ:1990:301:953-956).

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

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

Also in **1992**, the US Department of Health and Human Services produced a pamphlet on ME/CFS for the guidance of physicians (NIH Publication No. 92-484) which stated: *"ME/CFS symptoms overlap with those of many well-recognised illnesses, for example, lupus erythematosus (SLE) and multiple sclerosis. Psychiatric evaluations fail to identify any psychiatric disorders. Many people with ME/CFS have neurologic symptoms, including paraesthesiae, dysequilibrium and visual blurring. A few patients have more dramatic neurologic events such as seizures, periods of severe visual impairment, and periods of paresis. Evidence suggests that several latent viruses may be actively replicating more often in (ME)CFS patients 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 18th February **1993**, Professor Paul Cheney testified before the US FDA Scientific Advisory Committee as follows: *"I have evaluated over 2,500 cases. At*

*best, it is a prolonged post-viral syndrome with slow recovery. At worst, it is a nightmare of increasing disability with both physical and neurocognitive components. The worst cases have both an MS-like and an AIDS-like clinical appearance. We have lost five cases in the last six months. **The most difficult thing to treat is the severe pain. Half have abnormal MRI scans. 80% have abnormal SPECT scans. 95% have abnormal cognitive-evoked EEG brain maps. Most have abnormal neurological examination. 40% have impaired cutaneous skin test responses to multiple antigens. Most have evidence of T-cell activation. 80% have evidence of an up-regulated 2-5A antiviral pathway. 80% of cases are unable to work or attend school. We admit regularly to hospital with an inability to care for self***".

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

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

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

That same year (1995), UK researchers Geoffrey Clements et al reported that: *"Enteroviral sequences were found in significantly more ME/CFS patients than in the two comparison groups. The presence of the enteroviral sequences in a significant*

number of patients points to some role in ME/CFS. A variety of immunological disturbances have been reported for ME/CFS patients which may relate in some way to the enteroviral persistence. This study provides evidence for the involvement of enteroviruses in just under half of the patients presenting with ME/CFS and it confirms and extends previous studies using muscle biopsies. **We provide evidence for the presence of viral sequences in serum in over 40% of ME/CFS patients**" (J Med Virol 1995;45:156-161).

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

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

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

That same year, (1998) UK researchers Russell Lane and Leonard Archard published their findings of muscle abnormalities in response to exercise in ME/CFS patients: "The object of this study was to examine the proportions of types I and II muscle fibres and the degree of muscle fibre atrophy and hypertrophy in patients with ME/CFS in relation to lactate responses to exercise, and to determine to what extent any abnormalities found might be due to inactivity. **Muscle fibre histometry in patients with ME/CFS did not show changes expected as a result of inactivity. The authors note that one of these patients had an inflammatory infiltrate, and**

it would seem that inflammation and class I MHC expression may occur in biopsies from patients with ME/CFS. The authors note that this is of some interest, as they have argued previously that some forms of ME/CFS may follow a previous virally-mediated inflammatory myopathy". In general, following exercise, patients with ME/CFS showed more type I muscle fibre predominance and infrequent muscle fibre atrophy, unlike that which would be expected in healthy sedentary people. (JNNP 1998:64:362-367).

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

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

In 2001 an Australian study by Sargent, Scroop, Burnett et al from the Adelaide CFS Research Unit found that ME/CFS patients are not de-conditioned and that *"There is no physiological basis for recommending graded exercise programmes"*

(The Alison Hunter Memorial Foundation ME/CFS Clinical and Scientific Meeting, Sydney, Australia, December 2001).

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

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

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

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

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

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

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

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

(For conference reports, see <http://tinyurl.com/ylzwbmw> by Professor Charles Lapp from the US and Co-Cure NOT, RES: 2nd November 2004 by Dr Rosamund Vallings from New Zealand).

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

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

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

In 2006, Belgian researchers Nijs and De Meirleir reported on the observed associations between musculoskeletal pain severity and disability, noting that pain was as important as fatigue to ME/CFS patients: *“A few years ago, little was known about the nature of chronic musculoskeletal pain in ME/CFS. Research data gathered around the world enables clinicians to understand, at least in part, musculoskeletal pain in ME/CFS patients. Fear of movement (kinesiophobia) is not related to exercise performance in ME/CFS patients. From a pathophysiologic perspective, the evidence of a high prevalence of opportunistic infections is consistent with the numerous reports of deregulated and suppressed immune functioning in ME/CFS patients. Infection triggers the release of the pro-inflammatory cytokine interleukin-1 β which is known to play a major role in inducing cyclooxygenase-2 (COX-2) and prostaglandin E2 expression in the central nervous system. Upregulation of COX-2 and prostaglandin E2 sensitises peripheral nerve terminals. Even peripheral infections activate spinal cord glia (both microglia and astrocytes), which in turn enhance the pain response by releasing nitric oxide (NO) and pro-inflammatory cytokines. These communication pathways can explain the wide variety of physiological symptoms seen in ME/CFS. Experimental evidence has shown that ME/CFS patients respond to incremental exercise with a lengthened and accentuated oxidative stress response, explaining muscle pain and post-exertional malaise as typically seen in ME/CFS. In many of the published studies, graded exercise therapy has been adopted as a component of the CBT programme (i.e. graded exercise was used as a way to diminish avoidance behaviour towards physical activity). Unfortunately, the studies examining the effectiveness of GET/CBT in ME/CFS did not use musculoskeletal pain as an outcome measure (and) none of the studies applied the current diagnostic criteria for ME/CFS. From a large treatment audit amongst British ME/CFS patients, it was concluded that approximately 50% stated that GET worsened their condition. Finally, graded exercise therapy does not comply with our current understanding of ME/CFS exercise physiology. Evidence is now available showing increased oxidative stress in response to (sub)maximal exercise and subsequent increased fatigue and post-exertional malaise (Manual Therapy 2006: Aug. 11(3):187-189).*

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

Also in 2007, Klimas et al reported: *“Gene microarray data have led to better understanding of pathogenesis. Research has evaluated genetic signatures (and) described*

biologic subgroups. Genomic studies demonstrate abnormalities of mitochondrial function” (Curr Rheumatol Rep 2007:9(6):482-487).

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

In 2008, a collaborative study involving researchers from Belgium, the UK and Australia (published by J Nijs, L Paul and K Wallman as a Special Report in J Rehabil Med 2008:40:241-247) examined the controversy about exercise for patients with ME/CFS; the paper contains references showing adverse effects of GET:

“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; the other reference was Clark LV and White PD [J Mental Health 2005: 14: 237-252], in which Clark and White state that patients with ME/CFS are de-conditioned, and argue that: *“Patient education is necessary to inform patients of the positive benefit / risk ratio in order to improve acceptance and adherence”*). Nijs et al continue: *“Conversely, there is evidence of immune dysfunction in ME/CFS, and research shows further deregulation of the immune system in response to too-vigorous exercise, leading to an increase in fatigue and post-exertional malaise. It has been shown that even a 30% increase in activity frequently triggers a relapse (ref: Black CD, O’Connor, McCully K. Dynamic Medicine 2005:4:3). The severe exacerbation of symptoms following exercise, as seen in patients with ME/CFS, is not present in other disorders where fatigue is a predominant symptom. This post-exertional malaise is a primary characteristic evident in up to 95% of people with ME/CFS. It is possible that exercise at ANY intensity that exceeds*

an ME/CFS patient's physical capabilities may result in the worsening of symptoms. Early approaches to GET advised patients to continue exercising at the same level when they developed symptoms in response to the exercise. This led to exacerbation of symptoms and adverse feedback from patients and patient charities".

In 2008 a paper by Professor Julia Newton et al (Hollingsworth JG, Newton JL et al; Clin Gastroenterol Hepatol 2008;6(9):1041-1048) compared mitochondrial function in patients with primary biliary cirrhosis (PBC), patients with primary sclerosing cholangitis, patients with ME/CFS and normal controls; the authors stated that PBC is characterised in 95% of patients by autoantibody responses directed against the mitochondrial antigen pyruvate dehydrogenase complex (PDC). To define mitochondrial function in peripheral muscle during exercise, (31)P magnetic resonance spectroscopy was used.

Whilst the paper is chiefly concerned with mitochondrial dysfunction in patients with primary biliary cirrhosis (and the results clearly indicate mitochondrial dysfunction in patients with PBC, who showed excess muscle acidosis at higher levels of exercise), the authors state about ME/CFS patients: *"Interestingly, prolonged time to maximum proton efflux was also seen in the (ME)CFS control group, indicating that there are aspects of muscle pH handling that are abnormal in this important clinical group"*.

Professor Newton is Lead Clinician in the internationally renowned Cardiovascular Investigations Unit at the University of Newcastle, UK, which is the largest autonomic function testing laboratory in Europe; her work focuses on the role of the autonomic nervous system in the development of fatigue, specifically in primary biliary cirrhosis, but also in the pathogenesis of fatigue in ME/CFS. In her Conference pack for the ME Research UK International Research Conference held at the University of Cambridge on 6th May 2008, Professor Newton said: *"Recent results from a series of MR scans have shown impaired proton removal from muscle during exercise in patients with ME/CFS compared to matched controls. This has led us to hypothesise that fatigue arises due to impaired pH run off from muscle during exercise which is influenced by the degree of autonomic dysfunction"*.

In 2009, Light et al published evidence demonstrating that after moderate exercise, (ME)CFS patients show enhanced gene expression for receptors detecting muscle metabolites and that these were highly correlated with symptoms of both physical and mental fatigue and pain. The marked alterations in gene expression from circulating leucocytes of (ME)CFS patients after exercise

suggest that such alterations could be used as objective biomarkers, with ~ 90% of the (ME)CFS patients being distinguishable from controls using four of the genes measured. The authors have shown that 25 minutes of moderate exercise generates large and rapid increases in gene expression in leucocytes of (ME)CFS subjects but not in control subjects, findings which confirm previous suggestions that alterations in all parts of the HPA axis may mediate and sustain symptoms of (ME)CFS (The Journal of Pain 2009: doi:10.1016/j.pain.2009.06.003).

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

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

Conclusion

The above illustrations demonstrate just one aspect of the existing evidence-base about ME/CFS; they show that it is not a behavioural disorder or an aberrant illness belief, nor is it due to deconditioning as asserted by the Wessely School.

Documented abnormalities in other bodily systems are summarised in Section 2 of “Magical Medicine: how to make a disease disappear” (M. Hooper; <http://www.meactionuk.org.uk/magical-medicine.htm>).

Ten years after Jason et al’s call for better science (*“It is crucial for ME/CFS research to move beyond fuzzy recapitulation of the neurasthenia concept and to differentiate ME/CFS from other disorders”*. American Psychologist 1997;52:9:973-983), psychiatrist Dr Eleanor Stein from Canada repeated Jason’s message in her keynote lecture at the ME Research UK international conference in May 2007 in 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”*.

The Wessely School still is not listening; despite their many claims of “evidence-based medicine” about their own studies of “CFS/ME” (repeatedly shown to be methodologically flawed), they continue to deny the biomedical evidence-base that shows GET cannot help people with ME/CFS but which saves the medical insurance industry many millions of dollars.

Such is the difference between psychiatry and science.