

Documented pathology seen in ME/CFS that contra-indicates the use of Graded Exercise Therapy

Margaret Williams

23rd July 2009

The evidence-base of pathology that has been demonstrated in ME/CFS appears within a larger document that is already in the public domain, but is now provided as a 9 page separate item for ease of access.

The UK ME/CFS community may not yet be fully aware of the content of Dr Esther Crawley's presentation on 8th July 2009 to the Countess of Mar's "Forward -ME" group meeting held at the House of Lords. The Minutes of that meeting and Dr Crawley's power-point presentation are accessible at <http://www.forward-me.org.uk/8th%20July%202009.htm>

Of particular note are the following points made by Dr Crawley:

- The CCRNC (CFS/ME Clinical and Research Network and Collaboration, of which she is Chair) is a "multidisciplinary organisation which exists to promote and support the delivery of evidenced based treatment for children, young people and adults with CFS/ME throughout the UK" whose objective is **"To champion evidence-based approaches to the treatment of CFS/ME, such as those provided in the NICE guidelines"** and which will use "clinical expertise to inform healthcare policy" and will "provide training for clinicians and researchers from all disciplines involved in the diagnosis and treatment of CFS/ME".
- The CCRNC has an "Active training programme" and has "the ability to provide national training programmes".
- The CCRNC will "invite no more than four people drawn from National UK CFS/ME organisations **which explicitly support the aims and constitution of the organisation** to sit on the Executive committee as either observers or members".
- Its research strength is that it has the "Largest cohort in the world".
- Its strengths are "working together -- 600 clinicians and researchers, MRC, NIHR (National Institute for Health Research), Wellcome (*sic*), patient and carer reps, charity membership".

It is particularly notable that the Minutes record that when asked by Dr Charles Shepherd "whether, in the light of the widespread opposition to the NICE Guidelines, charities that were opposed to them would be invited to become members or associates of the CCRNC executive", Dr Crawley's response was: "In order to join the collaborative, charities would be expected to sign up to the evidence-based approach".

The only possible interpretation of this is that patients' charities are welcome to participate provided that they accept the behavioural modification interventions of CBT/GET recommended in the NICE Guideline (for which Dr Crawley was a member of the Guideline Development Group).

This would seem to be something akin to medical totalitarianism, especially given that Wessely School "evidence-base" upon which the NICE Guideline is predicated has been so stringently criticised by international ME/CFS experts.

See, for example: http://www.meactionuk.org.uk/JR_Statements_-_extracts.pdf

It is worth recalling that at the Royal Society of Medicine meeting on “Medicine and me: ME and CFS” held just three days later on 11th July 2009, MRC Professor of Clinical Immunopharmacology Stephen Holgate said that at the MRC, referees tend to reinforce the *status quo* and that he was not sure if his wish for an MRC inter-disciplinary group involving immunologists, neurologists and infectious diseases physicians would happen, which would seem to indicate that the psychiatrists’ stranglehold on MRC funding for biomedical research into ME/CFS is set to continue.

The Forward-ME Minutes also record that Dr Crawley said: “the reputation the CFS/ME charities had for infighting was not particularly helpful and prevented research and clinical involvement”.

Given that the “infighting” may have arisen because of the polarised views about the nature of ME/CFS, with the Government-funded charities (Action for ME and The Association of Young People with ME, to the latter of which Dr Crawley is Medical Advisor) supporting the NICE Guideline that is underpinned by flawed research, whilst other charities base their stance on the international evidence that shows the NICE Guideline to be seriously misinformed, it may be timely to look again at the following “evidence-base”.

Dr. Crawley stated that only those ME/CFS charities which agree to “sign up to the evidence based approach” are to be permitted to join her “collaborative”.

Given the volume of biomedical evidence that does not support Graded Exercise Therapy it would appear that in this instance signing up to an “evidence based approach” involves signing up to an approach that ignores most of the evidence.

Science is not furthered by a self-reinforcing “collaborative” determined to exclude dissenting voices; rather, a vigorous and honest dialectic is required. Medicine has no place for cabals and the lazy thinking they foster.

The “Forward-ME” Minutes record that Lady Mar said she hoped that Dr Crawley would “agree to continue to work with Forward-ME”; one can only wonder, sadly, just how far *backwards* her “Forward-ME” initiative will carry the UK ME/CFS community.

Evidence-based research showing pathology that contra-indicates the use of graded exercise in ME/CFS

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 .

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

Unique vascular abnormalities have been demonstrated in ME/CFS, with markers of oxidative stress. Oxidative stress is caused by highly reactive molecules known as free radicals circulating in the bloodstream of people with ME/CFS and results in cell injury. Oxidative stress levels are 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).

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**" (*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 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 parasthesias, 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, 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, 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**" (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).

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, once again demolishing the "de-conditioning" theory (JNNP: 2003;74:1382-1386).

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

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

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

At this Conference, findings were presented by a Belgian team (Nijs) which provided **evidence of underlying lung damage through intracellular immune dysregulation, with impairment of cardiopulmonary function** – elevated elastase levels could damage lung tissue and impair oxygen diffusion

across the alveoli in the lungs, potentially explaining decreased oxygen delivery to tissues that is seen in ME/CFS. (This presentation was singled out as being outstanding).

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

(For conference reports, see <http://www.drlapp.net/AACFS%20Meeting%20Summary.htm> 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 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 Guideline Development Group 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”.

The understanding of ME/CFS cannot be furthered by the continued ignoring of this evidence-base.