

# **Which Interventions are Helpful to Patients with 'CFS/ME'?**

## **A REVIEW OF THE EVIDENCE**

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### **INTRODUCTION : THE POLITICAL CONTEXT**

Following the publication of 'A Report of the CFS/ME Working Group'<sup>1</sup> to the Chief Medical Officer (England & Wales), considerable interest has been generated in the introduction and extension of services involving graded exercise [GE] programmes and cognitive behavioural therapy [CBT].

- This report stated that “*no management approach to CFS/ME has been found universally beneficial, and none can be considered a cure*”<sup>1</sup>.
- However, despite deep divisions within the Working Group regarding these interventions, the published report endorsed GE and CBT as strategies “*potentially beneficial in modifying the illness*”<sup>1</sup>.

The 'CFS/ME Working Group' was remitted to consider management and treatment. It was not asked to look at evidence pertaining to root cause. As a result, although the Group acknowledge that a variety of physiological abnormalities have been identified, the notion of a basically convalescent condition, mismanaged through prolonged inactivity, is implicit throughout much of the report without being subject to the critical scrutiny of relevant evidence.

In response to publication of the CFS/ME Working Group Report south of the border, the Scottish Executive sought “*to relate its findings to the NHS in Scotland*”<sup>4</sup> by setting up a ‘Short Life Working Group on CFS/ME’. As this group was not remitted to consider fresh evidence, nor to consider the evidence submitted to the English Chief Medical Officer’s [CMO’s] Working Group afresh, it is not surprising that the Short Life Working Group’s subsequent report also endorsed graded exercise and CBT as appropriate interventions.<sup>4</sup>

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## SUMMARY

Those who seek to respond appropriately to the needs of patients presenting with a diagnosis of 'Chronic Fatigue Syndrome' [CFS] – whether policy makers at political level, service planners, or providers on the ground – should be aware that evidence for the efficacy of behavioural interventions (graded exercise/activity and cognitive behavioural therapy [CBT]) is contradictory and by no means conclusive. (*see pages 5-13* )

Additionally, evidence exists which challenges the relevance of such approaches:

- A number of studies have identified physiological markers of exercise intolerance. In particular, it is important to be aware of the existence of evidence suggesting that exercise is positively harmful to certain patients, with the distinct possibility that the resultant damage is permanent. (*see pages 15,16*)
- Behavioural intervention strategies are predominantly predicated on the belief that patients are physically de-conditioned as a result of prolonged inactivity. However, there is evidence indicating that patients' physiological profiles and behaviour patterns are inconsistent with de-conditioning. (*see page 14*)
- This body of research evidence is in line with surveys of patients' experience which have consistently shown graded exercise to be the intervention most likely to leave the patient feeling worse than before. (*see pages 10, 11*)

***Such evidence fell outwith the purview of the English CMO's Working Group and subsequent Scottish Short Life Working Group.***

There is a tendency to assume that any negative effects following behavioural interventions such as exercise are simply due to inappropriate application (*see (1) pages 5-6*). This review has found no evidence to support this view.



## IMPLICATIONS FOR PRACTICE

The full range of relevant evidence strongly indicates that, if harm is to be avoided, any encouragement to undertake behavioural interventions such as CBT and graded exercise must be subject to appropriate pre-screening on a patient by patient basis. This is absolutely paramount in order to clarify the nature of the presenting problem. In particular, it is essential to differentiate the following two groups:

- Patients experiencing a simple fatigue state with concomitant problems brought about by physical de-conditioning through prolonged inactivity (behavioural interventions aimed at gradually increasing activity to normal levels may be helpful to this group);
- Patients suffering from a disorder involving neurological signs and symptoms, characterised by myalgia and post-exertional malaise (for patients in this category, the evidence clearly indicates that attempts to increase activity levels, and in particular to undertake aerobic exercise, are at best of peripheral relevance and at worst contra-indicated).

At the same time evidence of efficacy pertaining to other approaches should not be overlooked. In this context, it is relevant to note that, while no one treatment or management strategy may be universally effective, this is not to say that there is no value in therapies which help only some. Indeed, with the diagnostic parameters drawn very broadly, it would be astonishing if any one intervention was found to help all patients who currently fall under the umbrella diagnostic label 'chronic fatigue syndrome'. (Similarly, these broad parameters can only have hampered the search for a unique diagnostic marker).





# **THE EVIDENCE : PART I**

## **EVIDENCE ON MANAGEMENT AND TREATMENT**

The CMO's Working Group's terms of reference were specifically:

*“to review management and practice in the field of CFS/ME with the aim of providing best practice guidance for professionals, patients and carers to improve the quality of care and treatment for people with CFS/ME.”<sup>1</sup>*

Thus the Group was restricted to consideration of issues of care and treatment, with no remit to look at evidence on root cause in an attempt to define the basic nature of the condition.

### **SOME KEY POINTS**

#### **BEHAVIOURAL INTERVENTIONS**

The recommendations of the CMO's Working Group represent the results of an attempt to synthesise the Group's assessment of divergent evidence from three sources:

- **RESEARCH STUDIES** : The view that patients benefit from Graded Exercise and Cognitive Behavioural Therapy is based solely on the reported findings of a small number of published research studies.
- **PATIENT REPORTS** : On the other hand, surveys conducted by patient charities have consistently indicated that such approaches are detrimental to a considerable proportion of respondents, with rest (including bedrest) and pacing (finding an appropriate balance between activity and rest) emerging as the most helpful management approaches.<sup>2</sup>

- CLINICAL OPINION : Clinical opinion was found to be deeply divided.

*How might these - apparently conflicting - strands of evidence be reconciled?* Two possibilities have been suggested.

(1) Inappropriate Application of CBT/GE It should not simply be assumed that any negative effects reported by patients following behavioural interventions such as exercise are due to inappropriate application. Despite a lack of evidence this is, however, a fairly common perspective.

- For example: “... reported negative effects were probably due to either inappropriate advice on how to do graded exercise therapy (such as a doctor telling a patient to join a gym) or to patients trying this approach unsupervised by the appropriate professional.”<sup>14</sup> The authors refer to a survey by Action for ME in support of this contention.<sup>14</sup> However, the published findings from this survey provide no evidence whatsoever regarding what might account for the negative impact reported.<sup>14</sup>
- This is not the only example of this unfounded assumption. A letter written on behalf of the Chief Medical Officer (England and Wales) repeats the above quote almost verbatim, including reference to the Action for ME survey.<sup>14</sup>

(2) Inconsistency and Confusion over the Nature of the Condition A more likely explanation is that the patient groups involved in the various strands of research vary.

- The research on GE and CBT was not focussed on ME or strictly defined CFS, but aimed at investigating medically unexplained chronic fatigue, and selected participants using broad fatigue criteria. ME/strictly defined CFS and unexplained chronic fatigue are not the same.<sup>14</sup>
- Regarding the findings on adverse impact of Graded Exercise and CBT emerging from patient surveys, the CMO’s Working Group did recognise that these “clearly indicate that ... [the results of the research review] do not reflect the full spectrum of patients’ experience.”<sup>14</sup>

## OTHER INTERVENTIONS

The review of research findings commissioned by the CMO's Working Group<sup>24</sup> identified a total of 21 interventions – grouped under the categories immunological, antiviral, pharmacological, supplements, complimentary/alternative, behavioural, and 'other' – which showed some evidence of effectiveness in controlled trials.

- From among this group, behavioural interventions have risen to prominence because of the *number* of trials conducted, this reflecting their relatively greater success in securing funding.
- Other interventions have indeed shown evidence of efficacy, but mostly in a smaller number of studies.

Similarly, anecdotal reports suggest that some patients have experienced considerable improvement are possible following the use of therapies which have not yet been evaluated in trials (examples include vitamin B12 injections, and the calcium channel blocker nimodepene).

- If no is patent available (as in the case with the above examples), then there is no money to be made and therefore no incentive to conduct an appropriately controlled trial.

# GRADED EXERCISE AND COGNITIVE BEHAVIOURAL THERAPY:

## OVERVIEW OF WORKING GROUP ASSESSMENT OF EVIDENCE

The CMO’s Working Group’s Report’s endorsement of graded exercise and cognitive behavioural therapy is based on the published findings of seven research studies:<sup>2</sup> However, as well as a review of research results (known as ‘evidence based medicine’) the Group aimed to take into account two other lines of evidence – reports from patients and the opinions of clinicians among the Working Group – seeking to produce a synthesis of the three. Soundings from patients and clinicians were far from unanimous in endorsing these strategies. Indeed, both graded exercise and CBT were experienced by most patients who had tried them as harmful or inappropriate.

The sources of evidence used, as assessed in the published document,<sup>2</sup> are summarised in the table below.

SOURCE EVIDENCE	CMO’S WORKING GROUP ASSESSMENT OF EVIDENCE	
	GRADED EXERCISE	COGNITIVE BEHAVIOURAL THERAPY
RESEARCH FINDINGS	<i>“promising results”</i>	<i>“positive results”</i>
PATIENT REPORTS	<i>“substantial concerns exist regarding the potential for harm”... “adverse comments”</i>	<i>“wide variation in ... individual response” ... “only 7% of respondents found the therapy ‘helpful’”</i>
CLINICAL OPINION	<i>“disagreement”</i>	<i>“disagreement”</i>

It should be noted that a third management strategy was also highlighted as potentially beneficial. Pacing - “*an energy management strategy in which patients are encouraged to achieve an appropriate balance between rest and activity*” – was endorsed on the basis that, although “*research on pacing is sparse*” pacing had been found to be helpful in practice by a substantial proportion of patients who had tried it.<sup>4</sup>



## **THE EVIDENCE : SOURCE BY SOURCE**

The evidence from each of these three sources is considered in turn below.

### **CLINICAL OPINION**

In making their recommendations, the Working Group aimed to take into account “*consensus opinion among Working Group clinicians.*”<sup>2</sup> On the issue of the relevance and efficacy of graded exercise and cognitive behavioural therapy, however, there was no basic consensus. Rather,

*“Members of the Working Group expressed widely differing opinions on the potential benefits and disadvantages of these approaches.”<sup>2</sup>*

### **GRADED EXERCISE**

*“Clinical opinion - As with pacing, there is disagreement among clinicians about the value of graded exercise. Some clinicians consider graded exercise an effective therapy because of the evidence base, whereas others believe that CFS/ME involves a primary disease process that is not responsive to this type of approach, and that many of their patients are already functioning at or near to maximum levels of activity. However, the Working Group did agree that whenever graded exercise is being undertaken, activity levels should be initially based on current physical capacity. The programme should be mutually agreed between patient and therapist, it should be regularly adapted according to the clinical response, and patients should be carefully monitored to ensure that exertion does not exceed target levels.”<sup>2</sup>*

Commentary

Clinical opinion among the Working Group was deeply divided on the appropriateness of graded exercise for patients with 'CFS/ME'. Indeed, the above paragraph reflects a scenario akin to a group of clinicians fundamentally disagreeing as to whether or not a particular condition can be remedied by means of an operation, while agreeing that, should an operation be carried out, it should be conducted by a competent physician and with the patient suitably anaesthetised.

Furthermore, it is notable that those who did consider graded exercise to be “*an effective therapy*” did so “*because of the evidence base*” (presumably referring to evidence from research studies) and not on the basis of their clinical experience. This effectively ‘double counts’ the research evidence, rather than providing a separate strand of evidence from a different source. No evidence is presented regarding outcomes observed in clinical practice.



## COGNITIVE BEHAVIOURAL THERAPY

*“Clinical opinion - There was disagreement among clinicians as to the precise value and place of cognitive behavioural therapy, which partially reflected the varying models of the therapy and disease. However, there was agreement that when applied appropriately, with mutually agreed approaches and goals, it can undoubtedly benefit some patients. Some clinicians, using trial evidence and clinical experience, feel that it is beneficial to the majority of patients, whereas others feel it only benefits a minority. We also noted that misunderstanding, misplaced concern, and poor practice in this area could potentially undermine the beneficial application of this therapy or its principles in patients with CFS/ME.”*

### Commentary

Clearly this falls far short of a blanket endorsement of CBT. These disagreements and caveats are reflected in the subsequent recommendations regarding CBT in the Scottish Executive’s Short Life Working Group Report, which states:

*“It is not a technique that could or should be recommended to every patient.... Cognitive Behavioural Therapy may be helpful as an approach where the patients’ beliefs and concerns are central.”*

## PACING

*“Clinical opinion – Disagreement exists among clinicians who treat patients with CFS/ME over the value of pacing. Many clinicians, including some in the Working Group, routinely recommend the approach while others are less convinced of its benefits, their experience suggesting that pacing may prolong a patient’s illness. The Working Group noted that disagreement also exists over what is included in the term ‘pacing’.”*

## Commentary

Subsequent to the publication of the CMO's Working Group Report, it would appear that, among practising clinicians, pacing has been less enthusiastically endorsed than the other management strategies highlighted *i.e.* cognitive behavioural therapy and graded exercise. Furthermore, the disagreement over what constitutes effective pacing remains to be resolved: there is a fundamental distinction between a pacing strategy that is guided by the patient's ongoing assessment of what activity can be safely managed and how much 'rest' is needed, and an approach driven by pre-set goals and targets regarding the duration of activity periods and levels of activity to be undertaken. (The latter would be more accurately described as a form of graded activity; however, it would appear that this sort of approach is implied by some uses of the term 'pacing').

## **PATIENT REPORTS**

In a second line of evidence, the CMO’s Working Group heard reports from voluntary organisations, received findings of patient surveys, and held ‘Sounding Board’ events. The following table sets out findings of the patient survey which the Working Group Report drew on, in respect of the management strategies discussed below. It is notable that, from a total of eight specific treatments and behavioural management strategies covered by the survey, pacing and rest (including bedrest) were found to be the most helpful, while graded exercise and cognitive behavioural therapy were most likely to make the patient worse.

PATIENT EVIDENCE	MANAGEMENT STRATEGY	NO. WHO HAD TRIED	RESPONSE		
			HELPFUL	NO CHANGE	MADE WORSE
Most likely to help	REST, inc. BEDREST	2162	91%	8%	1%
	PACING ACTIVITIES	2180	89%	9%	1%
Least likely to help	GRADED EXERCISE	1214	34%	15%	50%
	COGNITIVE BEHAVIOURAL THERAPY	285	7%	67%	26%

### **GRADED EXERCISE**

Concerning patient reports, the CMO’s Working Group considered that: “*Graded exercise therapy can be effective in some individuals, but substantial concerns exist regarding the potential for harm.*” The results of a patient survey are quoted: Over a thousand respondents had tried graded exercise, half of whom reported that “*it had made their condition ‘worse’.*”

## Commentary

The Working Group Report wrongly refers to the figures quoted as deriving from a “*survey of people who were severely affected*”.<sup>23</sup> They are in fact findings from a membership survey by Action for ME,<sup>24</sup> a charity with a broad base not confined to severely affected sufferers. Findings from a membership survey conducted by the 25% ME Group<sup>25</sup>, which exists specifically to support those who are severely affected, were not included in the CMO’s Working Group’s Report. They show that the incidence of harmful effects was even higher among this group, with 82% of those who had undergone graded exercise reporting that it had made them worse. Furthermore: “*It is worth noting that some patients were not severely affected before trying GET.*”<sup>26</sup>

## **COGNITIVE BEHAVIOURAL THERAPY**

Patient reports are said to “... *suggest wide variation in the practice of and the individual response to cognitive behavioural therapy.*”<sup>27</sup> Results of the same patient survey are quoted: “*only 7% of respondents found the therapy ‘helpful’, compared with 26% who believed it made them ‘worse’. The remaining 67% reported ‘no change’*”.<sup>28</sup>

## Commentary

Findings from the survey of severely affected sufferers referred to above indicate a similarly poor response to cognitive behavioural therapy: only 7% of those who had tried CBT found it helpful.<sup>29</sup>

## **PACING AND REST**

The Working Group Report notes that “*Considerable support exists for pacing among patients and voluntary organisations...*”<sup>30</sup> and that this management approach had been found to be helpful in practice by a substantial proportion of

patients who had tried it. Quoting a survey of over 2,000 patients who had adopted pacing, it is noted that 89% - almost nine out ten - found it helpful. <sup>28</sup>

### Commentary

In contrast to the figures for GE and CBT, only 1% of those who had tried managing their condition by pacing activities reported a deterioration.

It is also notable that, in this same survey, a similarly high proportion (91%) found rest, including bedrest, helpful. However, no reference at all is made to the reported benefits of rest in the Working Group's published Report. <sup>29</sup>

## **RESEARCH STUDIES**

The third component of the evidence base on which the CMO's Working Group drew was a review of research studies, commissioned by the Policy Research Programme Division of the Department of Health and conducted by the NHS Centre for Reviews and Dissemination at the University of York. Regarding the published report of this review: <sup>4</sup>

*“The Key Group found the report to be a good review of evidence from randomised trials, but were concerned that the methodology used to compile the report was limited to quantitative evidence rather than also including studies of qualitative evidence.”<sup>4</sup>*

## **GRADED EXERCISE AND COGNITIVE BEHAVIOURAL THERAPY**

The findings of a combined total of seven randomised controlled trials on GE and/or CBT are assessed as “*promising*” and “*positive*” (respectively).<sup>4</sup>

### **Commentary**

It is notable that one of the seven studies<sup>4</sup> did not report a beneficial outcome, and that this study employed somewhat tighter criteria in the selection of participants. These criteria require cognitive and/or neuropsychiatric and/or immunological features to be present in addition to fatigue.<sup>4</sup> The authors of this study conclude:

*“Our results do not support the hypothesis that CFS would be adequately treated by DLE<sup>4</sup> and/or CBT. Continued efforts should be directed towards elucidating the pathophysiologic mechanism(s) underlying CFS in order to direct specific treatment.”<sup>4</sup>*

The remaining six studies reported beneficial outcomes. However, participants in these studies were selected using broad fatigue criteria. A co-author of the criteria most commonly used in these studies<sup>24</sup> describes them as follows:

*“British investigators have put forward an alternative, less strict, operational definition which is essentially chronic fatigue in the absence of neurological signs [but] with psychiatric symptoms as common associated features.”<sup>24</sup>*

It must be emphasised that these criteria do not specifically select people with ME. Furthermore, in the published reports of these studies the authors clearly and explicitly view their work as relating to medically unexplained chronic fatigue: this is not the same as ME, or strictly defined Chronic Fatigue Syndrome.<sup>25</sup>

It is also notable that these studies were characterised by the highest drop out rate of participants, in comparison with trials on various other types of treatment and management intervention (see below).<sup>26</sup>

The failure of randomisation to achieve its intended purpose *i.e.* to produce comparable control and intervention groups (for example, in terms of age and sex composition), should also be noted.<sup>27</sup>

The limitations of these trials have been discussed in the British Medical Journal<sup>28</sup> with the main points being summarised in MERGE’s response to the Working Group Report<sup>29</sup>.

## **OTHER INTERVENTIONS**

Only the research on graded exercise and cognitive behavioural therapy features in the CMO’s Working Group Report: no other research findings are mentioned.

### Commentary

As well as research on behavioural interventions, the review of research which fed into the deliberations of the Working Group identified randomised controlled trials on other types of intervention which had shown evidence of effectiveness. These are grouped into six categories:

- immunological
- antiviral
- pharmacological
- supplements
- complimentary/alternative
- ‘other’

A total of 18 such trials were identified, relating to 14 different management and treatment interventions. As these figures suggest, only a few had been the subject of repeated investigation. The authors of the review note that, where results are based on one or two studies only, this “*may limit the generalisability of the findings*”.<sup>4</sup> However, evidence of effectiveness from one or two studies only does not mean that an intervention has been found to be ineffective.

Against this background, however, it is notable that use of the immunological agent Immunoglobulin G, which demonstrated effectiveness in three out of four randomised controlled trials<sup>5</sup>, receives no mention at all in the discussion of therapeutic strategies in the Working Group Report.<sup>6</sup>





## SECTION II : EVIDENCE CHALLENGING THE RELEVANCE OF 'REHABILITATIVE' APPROACHES

The CMO's Working Group acknowledge that "*Research has demonstrated immune, endocrine, musculoskeletal, and neurological abnormalities.*"<sup>24</sup> However, the Working Group was not remitted to look into the significance of such findings. As a result, the ensuing report endorses graded exercise and cognitive behavioural therapy on the basis of research studies which assume that the condition can be overcome and patients rehabilitated by changes in behaviour, without subjecting these assumptions to the critical scrutiny of the full range of relevant evidence.

What follows is by no means a comprehensive or a systematic overview of such evidence. It is intended simply to present some pertinent examples of research findings which challenge the view that graded exercise or cognitive behavioural therapy (when aimed at increasing activity levels) may safely be considered to be relevant and helpful.

### EVIDENCE THAT ILLNESS IS NOT DUE TO DE- CONDITIONING

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*"Much of the current thinking about CFS and M.E. is driven by models of deconditioning. ... But what if exercise results in a huge delivery of free radicals, not because of disuse of muscle and deconditioning, but because there is something organically wrong with muscle metabolism? What value exercise in these circumstances? These are crucial questions, and it is important to remember that the current evidence [sic] for deconditioning is not based on scientific investigations of muscle but on suppositions about patients with 'fatigue'."*<sup>25</sup>

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*Acetylcholine Mediated Vasodilatation in the Microcirculation of patients with CFS.* VA Spence *et al.* Prostaglandins, Leukotrienes and Essential Fatty Acids 70 (2004) 403-407.

This research demonstrates that, most unusually for sick people, the response of the endothelium (the internal lining of the blood vessels) to acetylcholine is to dilate rather than to

contract. Dilation is characteristic of highly conditioned individuals such as athletes. *“Most diseases are accompanied by a blunted response to acetylcholine but the opposite is true for CFS. Such sensitivity is normally associated with physical training so the finding in CFS is anomalous and may well be relevant to vascular symptoms that characterise many patients.”*  
[page 403]

*Does the CFS involve the autonomic nervous system?* R Freeman & AL Komaroff, American Journal of Medicine 1997, 102, 4357-4364.

This study provides evidence that symptoms indicative of autonomic nervous system dysfunction are not related to psychiatric disorder and cannot be explained by deconditioning.

*Fatigue and activity patterns of people with CFS.* TL Packer *et al.* The Occupational Therapy Journal of Research 1997, 17, 3, 186-199.

Evidence from this study indicates that most patients with CFS do not spend the whole of the day time resting. It should be noted that very low levels of activity indeed are required for debilitating deconditioning to occur.



## EVIDENCE THAT EXERCISE IS CONTRA-INDICATED

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*“The most important thing about exercise is not to have them do aerobic exercise. I believe that even progressive aerobic exercise... is counter-productive. If you have a defect in mitochondrial<sup>a</sup> function and you push the mitochondria by exercise, you kill the DNA.”<sup>a</sup>*

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A number of studies focused on clearly defined patient populations have identified mitochondrial abnormalities. For example:

*Mitochondrial abnormalities in the post viral fatigue syndrome.* WMH Behan *et al.* Acta Neuropathologica, 1991, 83, 61-65.

In this study on a fairly homogeneous population, 80% of the biopsies showed evidence of structural damage to the mitochondria.

*The Postviral Fatigue Syndrome: an analysis of findings in 50 cases.* PO Behan *et al.* The Journal of Infectious Disease 1985, 10, 211 – 222.

This study revealed a variety of abnormalities in patients’ muscle biopsies, including mitochondrial abnormalities.

Talk by Prof. T Peters given at a meeting of microbiologists held at Cambridge University, April 1989, referring to various research studies.

*“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.”<sup>a</sup>*

*Enterovirus related metabolic myopathy: a postviral fatigue syndrome.* RJM Lane *et al.* Journal of Neurology Neurosurgery & Psychiatry 2003; 74: 1382-1386.

This study of skeletal muscle tissue provides evidence of impaired mitochondrial structure and function.

*Clinical studies of the postviral fatigue syndrome with special reference to skeletal muscle function.* Teahon *et al.* *Clinical Science*, 1988, 75, suppl. 18, 45.

Similarly, this earlier study showed significantly lower levels of intracellular muscle RNA content in sufferers, suggesting that these patients may have an impaired capacity to synthesise muscle protein, a finding which cannot be explained by disuse.<sup>4</sup>

## EVIDENCE OF ABNORMAL RESPONSE TO EXERCISE

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*“ ... the patients showed significant increases in symptoms following the [exercise] challenge; this is consistent with post-exertional relapse, a hallmark symptom of CFS.”* <sup>4</sup>

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*SPECT imaging of the brain: comparison of findings in patients with chronic fatigue syndromes, AIDS, dementia complex and major unipolar depression. RB Swartz et al. American Journal of Roentgenology, 1994, 120, 11, 972-973.*

*“... recent research using sophisticated brain scans (PET & SPECT) which measures metabolic activity generated during brain functions, have revealed a paradox. Whereas in healthy controls or people suffering with depression metabolism increases with exercise, in patients with ME it is diminished for a considerable period... Diminished metabolism in the brain stem (which also houses a nerve network, the reticular activating system, charged with keeping us awake and attentive) explains one of the most disabling symptoms of this illness – the unpredictable onset of central nervous system exhaustion following minor or physical or mental activity.”* <sup>5</sup>

*Demonstration of delayed recovery from fatiguing exercise in CFS. L Paul et al. European Journal of Neurology. 1999, vol. 6, pages 63-69.*

CFS patients were compared with healthy but sedentary controls. The results demonstrated that patients with CFS but not the sedentary controls failed to recover properly from a fatiguing exercise protocol, and that this failure was more pronounced a full 24 hours after exercise.

*“This exercise study provides a conclusive demonstration that recovery is significantly delayed in patients with CFS. [page 66]... the fact that the CFS patients do not recover to initial force levels at 24 hours, while the sedentary controls ... do, suggests that failure to recover is more related to the nature of CFS than to simple de-conditioning.”* [page 67]

*Excessive intracellular acidosis of skeletal muscles on exercise in the post viral exhaustion / fatigue syndrome: a <sup>31</sup>P-NMR Study. DL Arnold et al. Proceedings of third Annual Meeting of the Society for Magnetic Resonance in Medicine, New York, 1984, pages 12-13.*

*Skeletal muscle bioenergetics in the CFS.* PJR Barnes *et al.* Journal of Neurology Neurosurgery and Psychiatry 1993, 56, 679-683

*Reduced oxidative muscle metabolism in CFS.* KK McCully *et al.* Muscle Nerve. 1996, 19, 621-625.

These studies demonstrated that there is a significant abnormality in oxidative muscle metabolism with a resultant acceleration in glycolysis. (the breakdown of glucose by enzymes with the liberation of energy).

*Complement activation in a model of chronic fatigue syndrome.* B Sorevsen *et al.* Journal of Allergy and Clinical Immunology, August 2003; 112; pages 397-403.

This study looked at post-exercise immune changes. A significant increase in the split complement protein<sup>62</sup> C4a was detected in the CFS group six hours post exercise, correlating with post-exercise symptom reports. In healthy subjects, C4a generation is only stimulated at much higher exercise levels than those involved in this study,<sup>63</sup> and levels return to normal within three hours. The authors note that the exercise challenge allowed them to study CFS subjects in an exacerbated state of illness, as the patients subsequently showed significant increases in symptoms.<sup>64</sup>



## **APPENDIX: 25% ME GROUP SURVEY -**

### **MEMBERS' EXPERIENCES OF GRADED EXERCISE**

Regarding graded exercise, this paper makes reference to the findings of a membership survey carried out by the 25% ME Group (see page 10). The 25% ME Group have requested that readers should be made aware of the full text concerning respondents' experience of graded exercise as it appears in their survey report.

This reads:

*“By far the most unhelpful form of treatment was considered to be Graded Exercise Therapy (GET). This finding may surprise some readers, given the current medical popularity of this approach. However, these patients' perceptions are supported by data from previous experience: of the 39% of our members who had actually used Graded Exercise Therapy, a shocking 82% reported that their condition was made worse by this treatment. On the basis of our members' experiences we question whether GET is an appropriate approach for patients with ME. It is worth noting that some patients were **not severely affected before trying GET**. Thus, it is not only people with severe ME who may be adversely affected by this form of treatment.”*

[1](#) *A Report of the CFS/ME Working Group: Report to the Chief Medical Officer of an Independent Working Group*. London: Department of Health, 2002.

[2](#) *ibid.* page 34.

[3](#) *ibid.* page 45.

[4](#) *Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis (CFS/ME) Outline for Development of Services for CFS/ME in Scotland: Report of the Scottish Short Life Working Group*. Scottish Executive Health Department 2002, page 3.

[5](#) “Graded exercise therapy may be considered as one element in a care and management plan for a CFS/ME patient.” *ibid.* para 34, page 16; “CBT may be considered as one element in a care and management plan for a CFS/ME patient.” *ibid.* para 33, page 15.

[6](#) It would appear that this is what proponents of behavioural interventions mean by the term ‘Chronic Fatigue Syndrome’

[7](#) In other words, the key features of what used to be widely known as ‘Myalgic Encephalomyelitis’: the term is rarely used in medical or other official circles now.

[8](#) Hansard 5 February 1999.

[9](#) Research studies do not challenge these findings: rather, these management strategies lack a research base.

[10](#) *PACE trial – back it, say the organisers*. Dr. Peter White, Professor Michael Sharpe, and Professor Trudie Chalder. *ME Essential*, the magazine of The ME Association, Issue 92, October 2004, page 9.

[11](#) *Action for ME Membership Survey ‘your experiences’ questionnaire*. Wells, Action for ME, 2003.

[12](#) *Learning from experience*. *InterAction*, Issue 45, August 2003, pages 4-5. The article states that 40% of those who had tried GET “had not had professional guidance or support” [page 4], but does not provide information as to whether or not this group were more - or indeed less - likely to report a negative impact.

[13](#) Sent in reply to correspondence from Doris Jones concerning the MRC-funded PACE [Pacing, graded Activity, and Cognitive behavioural therapy: a randomised Evaluation] trial. Copy posted on [CO-CURE@LISTSDERVE.NODAK.EDU](mailto:CO-CURE@LISTSDERVE.NODAK.EDU) May19th 2005].

[14](#) The World Health Organisation classifies myalgic encephalomyelitis [ME] as a neurological disease, *i.e.* a disease of the central nervous system, in the International Classification of Diseases [ICD] 10, Section G93.3: it is also known as Chronic Fatigue Syndrome under this classification. Unexplained fatigue, on the other hand, is listed as a mental and behavioural disorder in ICD 10, at Section F48.0. No illness or condition may appear in more than one place in the WHO classification. (The UK Dept of Health formally accepts the ICD.)

[15](#) This statement is contained in an unpublished section of the report - ‘Annex 3: Patient evidence’, page 3.

[16](#) *The effectiveness of interventions used in the treatment/management of chronic fatigue syndrome and/or myalgic encephalomyelitis in adults and children*. A Bagnall *et al.* NHS Centre for Reviews and Dissemination, University of York, September 2002.

[17](#) Fulcher KY & White PD. *Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome*. *BMJ* 1997; 314: 1647-52.

Powell P *et al.* *Randomised controlled trial of patient education to encourage graded exercise in chronic fatigue syndrome.* *BMJ* 2001; 322: 387-92.

Wearden AJ *et al.* *Randomised, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome.* *Br J Psychiatry* 1998; 172: 485-92.

Sharpe M *et al.* *Cognitive behaviour therapy for the chronic fatigue syndrome: a randomised controlled trial.* *BMJ* 1996;312:22-6.

Deale A *et al.* *Cognitive behavior therapy for chronic fatigue syndrome: a randomized controlled trial.* *Am J Psychiatry* 1997;154:408-14.

Prins J *et al.* *Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial.* *Lancet* 2001;357:841-8.

Lloyd AR *et al.* *Immunologic and psychologic therapy for patients with chronic fatigue syndrome: a double-blind, placebo-controlled trial.* *Am J Med* 1993;94:197-203.

[18](#) *A Report of the CFS/ME Working Group: Report to the Chief Medical Officer of an Independent Working Group.* London: Department of Health, 2002, pages 46-49.

[19](#) *ibid.* pages 50-51.

[20](#) *ibid.* *Annex 5: Management of CFS/ME – evidence base*; Introduction, page 1. Again, this is an unpublished section of the report.

[21](#) *ibid.* page 45.

[22](#) *ibid.* page 47.

[23](#) *ibid.* page 49.

[24](#) *Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis (CFS/ME) Outline for Development of Services for CFS/ME in Scotland: Report of the Scottish Short Life Working Group.* Scottish Executive Health Department 2002, page 15.

[25](#) *ibid.* page 51.

[26](#) “*Harnessing the views of patients, parents, families, and carers to underpin the guidance was afforded high priority by the Working Group (Annex 3). Two ‘Sounding Board’ events were designed to capture some patient voices and to ensure that major stakeholders could identify pertinent issues.*” *ibid.* page 4.

[27](#) *Severely neglected: M.E. in the UK – Membership survey March 2001*, Action for ME. The full range of statistics quoted here are available only in an unpublished section of the Working Group Report - ‘*Annex 3: Patient evidence*’.

[28](#) *ibid.* page 47.

[29](#) *ibid.* page 47.

[30](#) *ibid.* page 47.

[31](#) *Severely neglected: M.E. in the UK – Membership survey, Action for M.E. March 2001.* (This survey employs a fairly broad definition of the term ‘severe’, with anyone housebound through illness deemed to be severely affected. Fewer than one in three respondents (30%) were housebound at time of survey, although – not surprisingly – most (89%) had been so affected at some time in the course of their illness.)

[32](#) *Severely Affected ME (Myalgic Encephalomyelitis) analysis report on questionnaire; 25% ME Group 1<sup>st</sup> March 2004.*

- [33](#) *ibid.* page 8. Readers are referred to the full text of this survey report as set out on page 17 below.
- [34](#) *A Report of the CFS/ME Working Group: Report to the Chief Medical Officer of an Independent Working Group.* London: Department of Health 2002, page 49.
- [35](#) *Severely neglected: ME in the UK – Membership survey March 2001*, Action for ME.
- [36](#) *Severely Affected ME (Myalgic Encephalomyelitis) analysis report on questionnaire; 25% ME Group 1<sup>st</sup> March 2004.*
- [37](#) *A Report of the CFS/ME Working Group: Report to the Chief Medical Officer of an Independent Working Group.* London: Department of Health, 2002, page 51.
- [38](#) *Severely Neglected: ME in the UK – Membership survey March 2001*, Action for ME.
- [39](#) This statistic is contained in an unpublished section - '*Annex 3: Patient evidence*' (page 3).
- [40](#) *The effectiveness of interventions used in the treatment/management of chronic fatigue syndrome and/or myalgic encephalomyelitis in adults and children.* A Bagnall *et al.* NHS Centre for Reviews and Dissemination, University of York, September 2002.
- [41](#) Again, this statement is from an unpublished annex to the Working Group Report. It can be found in Annex 5 – *Management of CFS/ME – evidence base*, page 1.
- [42](#) *ibid.*, pages 46 and 48, respectively
- [43](#) *Immunologic and Psychologic Therapy for Patients With Chronic Fatigue Syndrome: A Double-Blind, Placebo-Controlled Trial.* A. Lloyd *et al.* The American Journal of Medicine Volume 94 Feb. 1993 pp197-203.
- [44](#) Lloyd A, Wakefield D, Boughton C, Dwyer J. *What is myalgic encephalomyelitis?* Lancet 1988; 1: 1286-7
- [45](#) An immunological therapy
- [46](#) *Immunologic and Psychologic Therapy for Patients With Chronic Fatigue Syndrome: A Double-Blind, Placebo-Controlled Trial.* A. Lloyd *et al.* The American Journal of Medicine Volume 94 Feb. 1993 pp197-203. (quote from p202).
- [47](#) Sharpe M, Archard L, Banatvala J. *A report: chronic fatigue syndrome: guidelines for research.* J R Soc Med 1991; 84: 118 – 21: commonly referred to as the 'Oxford criteria'.
- [48](#) *Postviral syndrome and psychiatry.* AS David, British Medical Bulletin 1991; 47:4:966-988).
- [49](#) See note 7 (page 4 above).
- [50](#) *The effectiveness of interventions used in the treatment/management of chronic fatigue syndrome and/or myalgic encephalomyelitis in adults and children.* A Bagnall *et al.* NHS Centre for Reviews and Dissemination, University of York, September 2002, page 38.
- [51](#) Randomised controlled trials are widely viewed as the 'gold standard' of research. However, the effectiveness of the control mechanism is considerably undermined if the distribution of subjects results in substantial differences between intervention and control groups. While random allocation works well for large scale studies, it is much less likely to produce appropriately matched groups where a study involves relatively small numbers. When undertaking a small scale study it is more appropriate to deliberately allocate subjects in such a way as to produce matching groups for key characteristics - such as age and sex – rather than rely on random allocation to produce this outcome.
- [52](#) BMJ 1997; 315: 947 and electronic responses to BMJ 2001; 322: 387-92.

[53](#) *Unhelpful Counsel? MERGE's response to the Chief Medical Officer's Working Group Report on CFS/ME*, April 2002, page 18. 'MERGE' stands for 'M.E. Research Group for Education and support'. The organisation is a national charity which commissions and funds biomedical research into the underlying causes of M.E.

[54](#) *ibid.* page 44.

[55](#) *ibid.* page 45. (This is exactly the same incidence as pertained to CBT).

[56](#) *A Report of the CFS/ME Working Group: Report to the Chief Medical Officer of an Independent Working Group*. London: Department of Health, 2002, pages 45-51.

[57](#) *ibid.* page 21.

[58](#) Dr Vance A. Spence, Chairman of MERGE (a national M.E. research charity which commissions and funds biomedical research), writing in *InterAction*, the journal of Action for ME, Issue 50, 2004.

[59](#) "Remember that muscles remain constantly in tone if you only move between bedroom and bathroom." From *Time to put the exercise cure to rest*. E Dowsett, available on the 25% MEGroup website. <http://www.25megroup.org/Information/Medical/exercise>

[60](#) Mitochondrial cells make energy to power the body.

[61](#) Professor Paul Cheney, Director of the Cheney Clinic, North Carolina, USA; a lecture given in Orlando, Florida, 5-7th February 1999 at the International Congress of Bio-energetic Medicine. As of February 1993 Professor Cheney had clinically evaluated over 2000 cases [as stated in *InterAction*, the journal of Action for ME, Issue 14, autumn 1993, page 40]. He can reasonably be considered to be one of the world's leading experts on this condition.

[62](#) As reported in the ME Association Newsletter, Autumn 1989, page 16.

[63](#) As reported in the ME Association Newsletters summer 1989, page 6, and autumn 1989, page 24.

[64](#) *Research update*, *InterAction*, the journal of Action for ME, Issue 47, February 2004, page 8: referring to the research by Sorevsen et al. noted below.

[65](#) Commentary on this research from *Time to put the exercise cure to rest*. E Dowsett, available on the 25% MEGroup website. <http://www.25megroup.org/Information/Medical/exercise>

[66](#) <sup>31</sup>P-Nuclear Magnetic Resonance permits continuous 'live' assessment of muscle metabolism.

[67](#) Complement proteins are a key component of the general immune system response to infection.

[68](#) CFS and healthy control groups exercised for 20 minutes on stationary bicycles at 70 per cent of their predicted maximum work loads.

[69](#) As reported in *Research Update*, *InterAction*, the journal of Action for ME, Issue 47, February 2004, page 8.