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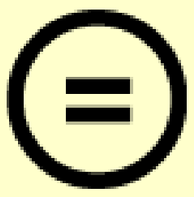

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PHYSIOLOGICAL AND PSYCHOLOGICAL RESPONSES OF PATIENTS WITH CHRONIC FATIGUE SYNDROME TO REGULAR PHYSICAL ACTIVITY

by

Kathy Fulcher

A Doctoral Thesis

Submitted in partial fulfilment of the requirements
for the award of Doctor of Philosophy of Loughborough University

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ABSTRACT

Background Chronic fatigue syndrome (CFS) is characterised by chronic disabling fatigue affecting physical and mental function, whereby sufferers can enter a cycle of symptoms, avoidance, inactivity, decreased exercise tolerance, fatigue and depression. There are no established treatments for CFS and sufferers are often advised to rest, which can lead to physical deconditioning and few studies have measured both physiological and psychological parameters in the same group of patients. The aims of this study were to compare physiological and psychological measures on CFS patients with those of healthy, sedentary individuals and then to monitor and examine the efficacy of a graded exercise programme and compare this with a control treatment of relaxation and flexibility training on selected physiological and symptomatic parameters in patients with CFS.

Methods Sixty-six subjects with the chronic fatigue syndrome, who had neither a psychiatric disorder nor significant sleep disturbance, and 30 healthy sedentary controls and 10 depressed patients were recruited. Physiological measurements included a treadmill walking test for assessment of maximum aerobic capacity and submaximal exercise tolerance, resting lung function, twitch interpolated isometric quadriceps strength, body fat and self-rated psychological questionnaires assessed physical and mental fatigue, general health, physical and social function, depression and anxiety. Equal numbers of the CFS patients were then randomly allocated to 12 weeks of either graded aerobic exercise or flexibility exercises and relaxation therapy. The main outcome measure was the self-rated clinical global change score, considering "very much better" or "much better" as clinically important improvements. Other outcome measures included fatigue, mood and functional capacity as well as physiological measures. Those subjects who completed the flexibility programme were invited to cross over to the exercise programme afterwards. All subjects were reassessed physiologically and symptomatically immediately after completion of either treatment and 3 months after completion, with a postal follow-up 1 year after completion.

Findings Compared with healthy sedentary controls CFS patients had a significantly lower peak oxygen uptake, test duration, post-test blood lactate, peak heart rate and isometric leg strength, along with higher levels of physical and mental fatigue and a lower ratings on general health and functional capacity. The CFS and depressed patients were equally deconditioned, but CFS patients differed in mental and emotional health status and had a lower perception to functional capacity. On the treatment trial, 4 subjects receiving exercise

and 3 having flexibility dropped out before completion. 16/29 (55 %) of subjects rated themselves better after exercise, compared to 8/30 (27 %) who completed the flexibility treatment (X^2 = 3.9, 1 df, p = 0.03)(28 % difference, 95% ci = 4, 52%). Analysing by intention to treat gave similar results. No significant differences were observed in any physiological measures between the two groups at baseline. After treatment significant differences were observed in peak VO_2, maximum ventilation and in heart rate and perceived exertion rating at all submaximal levels stages in the walking test, between the groups after treatment. Significant intergroup differences were observed in physical and total fatigue, physical function and general health after treatment. 12/22 (55 %) of those subjects who crossed over from flexibility to exercise rated themselves better after completing the exercise treatment. 32/47 (68 %) of subjects felt better three months after completing exercise treatment, with physiological and symptomatic improvements maintained. 36/47 (76 %) subjects rated themselves better 18 months after starting the exercise treatment.

Interpretation These findings support the use of appropriately prescribed aerobic exercise in the management of patients with the chronic fatigue syndrome.

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Finally, thanks are due to the volunteers and the patients themselves, who I hope benefitted from their involvement and are continuing to do well.

Very finally, a special thanks are due to my parents who have given me the determination and courage to persevere with my goals and who encouraged and supported me throughout the study and in everything I do.

This thesis is dedicated to the memory of my father, who has been the single most important influence in my life, and whom I am proud to have known.

Unless otherwise indicated the work contained in this thesis is that of the author and has not been previously submitted for another degree in this or any other University

Part of the work contained in this thesis has been published in the following scientific journals:

Published Communications

Fulcher,K.Y. & White,P.D. A controlled trial of a graded exercise programme in patients with the chronic fatigue syndrome. (Abstract). European Journal of Applied Physiology and Occupational Therapy, 69(3); S35, 1994

Fulcher, K.Y & White, P.D A comparison of physiological and psychological parameters between CFS patients and healthy sedentary controls. (Abstract)
Journal of Chronic Fatigue Syndrome, 2; 148 –149, 1996.

Paper

Fulcher, K.Y & White, P.D. A randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome
British Medical Journal, 314; 1647 – 1652, 1997.

Personnel involved in the study

The initial psychiatric and symptomatic screening for the Chronic Fatigue Syndrome patients and depressed patients was carried out by a qualified psychiatrist at the Department of Psychological Medicine, St. Bartholomew's Hospital.

The introduction and explanation of the physiological assessment, and all physiological assessments for all groups (patients and voluntary control subjects) were carried out by the author.

On reassessments the physiological tests and administration of psychological questionnaires was carried out by author.

Analysis of all results, physiological and psychological was carried out by the author

Introductory exercise stretching sessions and all relaxation sessions were done by the author as well as the weekly exercise prescription.

In order to avoid experimenter bias and to extend the personnel involved in dealing with the patients, 2 other exercise physiologists at different stages in the study were involved in carrying out the weekly exercise sessions with the patients under the supervision of the author.

In the same week as the psychological physiological re-assessments, an appointment was made for each CFS patient with the psychiatrist to complete the Clinical Global Impression change scale (CGI) and the Structured Clinical Interview for DSM-III-R), both of which are required to be conducted with a psychiatrist.

The one-year follow up was administered by the author, as was collation and analysis of these results.

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CHAPTER ONE: INTRODUCTION

Several chronic medical conditions involve considerable bedrest and inactivity, whether in the rehabilitation and recovery from disease or as a consequence of long-term illness. As early as 1949, Taylor demonstrated that bedrest leads to severe deconditioning in healthy, athletic young men (Taylor, 1949), and later Saltin (1968) recorded a 30% loss of aerobic capacity after only 3 weeks of bedrest in trained individuals. In the same manner, chronic disease typically leads to a cycle of decreased physical activity (often bedrest), which results in deconditioning and a cycle of symptoms associated with decreased functional capacity and increased fatigue, which further reduces physical activity. Disease exacerbations tend to speed up this debilitative cycle. This can also have adverse psychological consequences, as individuals develop a dependency on others for support which can, in turn, lead to depression, frustration and anxiety, and further avoidance of activity. To break these cycles, exercise therapy is increasingly being advocated in the treatment of several chronic illnesses, such as arthritis, osteoporosis, diabetes and chronic hypertension (Basmajian & Wolf, 1990; Carlucci, 1991). Exercise therapy can have very positive and beneficial psychological effects as well as the well-documented physiological effects (Moses, 1989; Morgan, 1985). Some studies have also shown exercise to be equally as effective as traditional psychotherapy and drug therapy in the treatment of depression (Martinsen, 1990).

Although disuse and ageing are not synonymous, they do share common attributes, and much recent research has demonstrated the benefit of structured physical activity programmes with the elderly (Mengshael, 1995), which suggests the potential beneficial effects of a similar approach with certain chronic illnesses.

Recent research points to a need for a more dynamic approach towards treatment of chronic illness with a move away from long term rest towards progressive exercise (Frost et al, 1995; Goldstein et al, 1994). Few studies have measured physiological and psychological changes associated with a progressive, graded exercise programme in the same group of patients.

This thesis discusses a study which examines both the physiological, psychological and symptomatic measures before and after a graded exercise programme in a group of patients diagnosed as having Chronic Fatigue Syndrome (CFS). The key feature of this illness is chronic or recurrent debilitating fatigue exacerbated by physical and mental effort and associated with a prolonged recovery time. The fatigue experienced after physical effort is greater than would be expected from the intensity of the activity and greater than previously experienced by the patient. This state can last up to several years. There are no specific diagnostic tests and several potential causes have been proposed for CFS.

The triggering event is frequently an infection, particularly of viral origin, but other factors may potentiate the disease. There are numerous reports on the coexistence of chronic fatigue and depression and other psychiatric disorders, and some CFS patients have a history of psychiatric disorders prior to the fatigue. Another is that depression is a secondary effect of the disability caused by CFS, and this prolonged fatigue can begin a cycle of attributional and cognitive factors fuelling avoidant behaviour. Patients can then enter into a vicious circle of symptoms, avoidance, inactivity, fatigue and depression.

Inactivity is known to have a detrimental effect on muscle, as well as on respiratory and cardiovascular functions. The evidence to date shows no abnormalities in cardiovascular or peripheral muscle response other than what would be expected as a result of deconditioning. In addition, CFS patients tend to have an altered perception of effort with any physical exertion, which may be associated with a profound fear of exacerbating the symptoms and causing a relapse, should they over-exert themselves.

Initially we compared a group of CFS patients with healthy sedentary individuals and a group of patients suffering from major depression, on both physiological and psychological measures. This comparison was to determine whether CFS patients were physiologically deconditioned (compared to healthy individuals) but dissimilar to depressed patients (on the psychological measures), an illness with which they are frequently labelled. The ensuing

hypothesis was that a graded and structured exercise programme should have positive physiological and symptomatic and outcome effects in CFS patients.

Since the causes and duration of the chronic fatigue are varied, this approach must be individually tailored, graded, realistic and include a very gradual return to physical activity. The exercise should be aerobic in nature since cardiovascular and respiratory functions are predominately associated with deconditioning. This would support the use of graded exercise therapy as a valid treatment for patients suffering from chronic fatigue syndrome.

The exercise treatment was compared with a more frequently recommended treatment for this condition of relaxation and flexibility. Initial baseline measures examined aerobic capacity, isometric leg strength, perceived effort rating, blood lactate response to activity and body composition, as well as symptomatic measures of physical and mental fatigue, sleep, anxiety, depression and general health perceptions. The CFS patients were randomly allocated into either a graded aerobic exercise or flexibility and relaxation treatment and reassessed on all measures after 12 weeks. Those initially on the flexibility and relaxation programme could cross over to the exercise treatment after the first reassessment. The long-term effectiveness of the programme was determined by a full reassessment at 3 months after treatment completion and a postal follow-up 1 year later. Outcome of treatment was determined by patient rating of improvement as well as repeated physiological and symptomatic measures.

Dept. of Psychological Medicine

Exercise Physiology Laboratory

Subject screening
Baseline symptomatic questionnaires
SCID analysis

Groups: Healthy sedentary controls
Depressed patients
CFS patients

Week No.	
1	Physiological assessment (1)
2	Physiological assessment (2) **A + B** CFS patient randomization n = 33 → **Exercise group**: 12 x weekly exercise sessions n = 33 → **Flexibility group**: 12 x weekly flexibility sessions **C + D**
15	Physiological reassessment Symptomatic questionnaires
27	**D**: Cross-over group 12 x weekly exercise sessions **D**: Physiological & symptomatic Reassessment **E+F**
27 or 39	Physiological reassessment Symptomatic questionnaires - 3 month follow-up results
75 or 87	**G**: 1 year postal follow-up activity/work/fatigue questionnaire

Clinical interview & improvement rating

Clinical interview & improvement rating

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CHAPTER TWO: REVIEW OF LITERATURE

2.1 Definition

Patients who complain of chronic disabling fatigue of uncertain cause have received much attention in recent years. The controversial condition does not lend itself well to normal medical concepts, with the complex clinical presentation of patients describing a variety of muscular, neurological, psychological and autonomic symptoms in addition to fatigue. Numerous outbreaks have been reported over the last 100 years. The most famous of these, which was later labelled as myalgic encephalomyelitis, was one involving 292 members of staff at the Royal Free Hospital, London, in 1955 (Medical staff, 1957), who complained of weariness and muscle pain. Before this an epidemic of "neuromyasthemia" affected 198 employees of Los Angeles County General Hospital, who complained of similar symptoms (Gilliam, 1938). Other labels previously given to a similar ranges of symptoms include chronic infectious mononucleosis, postviral fatigue syndrome, fibrositis-fibromyalgia, post-infectious fatigue syndrome, neuromyasthemia and chronic Epstein-Barr virus infection (Wessely, 1993).

Research into the condition has been approached from several medical and scientific disciplines, which are partially responsible for the disparity of terms. In an attempt to address this problem of numerous labels for an apparently identical range of symptoms, Holmes and colleagues (1988) came up with the label of Chronic Fatigue Syndrome (CFS), which has the advantage of referring directly to a major symptom, while making no assumptions about aetiology. They also proposed an operational definition for the syndrome (Appendix A). The fatigue must be idiopathic, severe and chronic, but patients must also have at least eight of eleven specified symptoms, or at least six of the symptoms together with at least two of three specified signs. However, this definition was considered too complicated in application and restrictive in scope. Lloyd et al (1988) developed less strict criteria, but these too were considered too restrictive, involving tests of cell-mediated immunity. In an attempt to remove these obstacles and develop a more workable definition, a meeting of research

workers with a known interest in the field was convened. This British consensus meeting in Oxford in 1990 developed a simpler and wider definition of two broad syndromes: Chronic Fatigue Syndrome and Post-Infectious Fatigue Syndrome (Sharpe et al, 1991).

From this meeting the Chronic Fatigue Syndrome (CFS) was defined as characterised by severe, disabling fatigue as the principal symptom. The fatigue should be of definite onset that is not life long. It should have been present for a minimum of six months and for more than 50% of the time. The fatigue must affect physical and mental functioning and other symptoms, such as myalgia, mood and sleep disturbance (but a clinical sleep disorder), may be present. Patients excluded from the definition are those with established medical conditions known to cause fatigue as well as those with a diagnosis of schizophrenia, proven organic brain disease, substance abuse, manic depressive illness and eating disorders. Patients with other psychiatric disorders such as anxiety or depressive illness need not necessarily be excluded. The Post-infectious fatigue syndrome (PIFS) is characterised by the same symptoms as CFS but, in addition there must be definite evidence of an infection at onset or presentation and the syndrome must be present for a minimum of 6 months after the onset of infection (White et al, 1995; Fukuda et al, 1994).

2.2 Aetiology

A definitive cause for the chronic fatigue syndrome has not yet been established and both organic and psychological factors have been implicated. Those worthy of discussion in this review include viruses, immune dysfunction, psychological problems, psychiatric disorders, sleep disorders, muscle dysfunction and inactivity.

2.2.1 Viruses

Some groups believe that CFS is a chronic virus infection and effective treatment must await the development anti-viral therapy. The proposal of a viral cause arose from evidence that the onset of symptoms, in a large proportion of patients, was preceded by an influenza type illness. The viruses incriminated were predominantly enteroviruses in Britain (Youssef et al, 1988) and Epstein-Barr virus (EBV) in America (Straus et al, 1993). Epstein-Barr virus

infects over 95% of humans, most often without producing illness. Infectious mononucleosis may develop when the virus infects an adolescent or young adult. Results of several studies in the USA (see review, Straus, 1993) reveal that EBV-specific serologies were not helpful in the diagnosis of patients with chronic fatigue. There is no good evidence that higher levels of antibodies reflect more frequent reactivation of EBV. In a prospective study examining the relationship between viral infection and fatigue, White (1995a&b) found that the prevalence of fatigue was significantly more common after EBV infections than after upper respiratory tract infections, 6 months after onset. However, further evidence from two seroepidemiological surveys indicates that EBV is unlikely to be an aetiologic agent in most cases of CFS (Horowitz, et al, 1985, Hellinger, 1988). Cytomegalovirus infection has also been proposed as a trigger for chronic fatigue, but as with EBV, there is no evidence of active CMV in patients with chronic fatigue, although both infections may precede the syndrome. Initial findings on herpesviruses indicate a higher prevalence of Human herpes virus 6 (HHV6) in the serum of chronic fatigue syndrome patients compared to controls (Saxinger et al, 1988). However HHV6 has also been recovered from healthy patients (Buchwald et al, 1992) and therefore, its role as a causative factor in CFS is, as yet, unconfirmed.

Enteroviruses are very common in this country and are generally associated with 'summer colds'. Although they are highly infectious, most people eliminate the infection within a few days. A small minority may retain the infection and may go on to develop CFS symptoms. McCartney et al (1986) described a widespread epidemic of an enterovirus. A few of those infected appear to be unable to eliminate the virus rapidly, and develop a chronic condition. Mowbray (1991) observed that muscle fatigue on exercise was a feature of enteroviral patients more so than EBV patients, suggesting that the latter group tend to show lethargy and inanition and do not wish to exercise, in contrast with the very poor exercise tolerance seen normally in enteroviral patients.

The early serological studies of neutralising antibodies to coxsackie viruses suggested a possible role for these agents in some cases (Behan et al, 1985), but their use as a diagnostic

test was not valid because of the frequency of asymptomatic infections among the population (Miller et al 1991). Yousef et al (1988) suggested that the detection of enteroviral antigen VP-1 was associated with chronic symptomatic infection in up to 45% of their sample at four months. However, Lynch and Seth (1989) found a positive antigen test in 30% of both hospital controls and CFS patients, with no differences between the groups. This evidence suggested that there was no connection between the severity of symptoms and presence of the antigen (Halpin & Wessely, 1989). This group also found similar rates of VP1 in depression and CFS. Behan et al (1993) detected enteroviral genome sequences in muscle biopsies from cases of PIFS, and suggested that it is the presence of persistent virus in muscle, as opposed to peripheral blood, that is associated with CFS. This may cause mitochondrial changes that lead to cell dysfunction similar to that seen in mitochondrial abnormalities (Behan et al, 1993). Their results await replication. Evidence exists that there is a specific, self-limiting fatigue syndrome following infection with EBV (White et al, 1995) while Hoptof et al (1996) found an increased risk of developing CFS after viral meningitis. Psychiatric disorder and prolonged convalescence were also found to be predictors of CFS. Both of these recent studies suggest that common viral infections do not trigger CFS but several infections do, whereby they act as a stressor rather than by any particular molecular process (Cleare & Wessely, 1996).

2.2.2 Immune Dysfunction

Both cellular and humoral immune mechanisms participate in the host response to viral and other infections. The first line of defence involves natural killer cells. The accompanying response involves cytotoxic T cells and cytokines and neutralising antibodies. Immunological studies in patients with CFS have examined each of these aspects of the immune response to antigen and a wide variety of immunological changes have been reported (For review see Buchwald & Komaroff, 1991; Lloyd et al, 1993). As with studies examining persistent virus infection as a causative factor in CFS, those examining immune dysfunction report positive evidence in some but not all CFS cases. There is evidence of immunologic dysfunction; some parameters reflect deficient function while others indicate hyperactivity. It has not been

shown that these immunologic findings explain the symptomatology of CFS or correlate with changes in symptoms over time (Buchwald & Komaroff, 1991). The data on immune dysfunction has been somewhat limited to date both by the heterogeneity within the patient groups studied and by the lack of standardisation of the available assays. Lloyd et al (1993) has suggested that, since the evidence establishing a causal link between abnormal immunity and CFS has not been found, the alterations are secondary to an undefined underlying disease process or co-factor.

Numerous other immune system abnormalities have been reported in CFS patients, including functional deficiency in natural killer cells (Caligiuri, 1987). This has been referred to as chronic fatigue immune deficiency syndrome and is characterised by fatigue, remittent fever, and lowered natural killer cell activity.

2.2.3 Psychiatric Disorders

Some authors believe that CFS is predominantly a depressive disorder (Greenberg, 1990) and is best treated with antidepressive drug therapy. Both fatigue (physical and mental) and muscular pain are prominent symptoms of depressive disorders (Stoeckle & Zola, 1964), so that CFS patients' symptoms are sometimes difficult to distinguish from those of depressive disorder patients (Wessely & Powell, 1989). The evidence suggests that the depressive disorder accounts for the symptoms and disability attributed to CFS in some cases (Lane et al, 1991).

A link has been established between fatigue and psychological distress. A large community survey found that 20% of women and 14% of men complained of significant fatigue and that about 50% of these also had symptoms of depression (Chen, 1986). David (1991) reviewed thirteen published reports, which had recorded psychiatric symptoms and diagnoses in chronically fatigued patients. These included depressive, panic and anxiety disorders and somatization. Not all of these studies used standard criteria for CFS but Lane et al (1991) did use these established criteria in their study of 200 adult patients. The 60 patients with CFS had similar likelihoods of current psychiatric disorders, active mood disorders when

compared with fatigued control subjects. They concluded that CFS patients have a high prevalence of unrecognised, current psychiatric disorders, which often preceded their fatigue syndrome. Ray (1991) also found that a significant percentage of patients with fatigue appeared to have a psychiatric disorder, with major depression being the most common disorder. Several questions arose from her review. The first questioned the appropriateness of using standard procedures for determining depression in these patients, since CFS patients do not present with depression or a psychiatric disorder as their primary symptom and it may be secondary to or be a consequence of the prolonged fatigue. Secondly, there is a possibility that a depressive illness may form part of the symptomatology of an organic illness. Also, any chronic illness can produce a psychological challenge, and patients who are depressed may be so as a reaction to their illness. However, there is evidence that psychiatric problems precede the onset of fatigue in some patients. In the patient group studied by Taerk et al (1987), 50% had a major depressive episode prior to the development of "neuromyasthemia", while Kruesi et al (1989) concluded that psychiatric problems were more likely to predate CFS than to follow. Similarly, Lane et al (1991) produced evidence that depression generally preceded fatigue or had a simultaneous onset in a group of 60 CFS patients who were also more likely to have somatization disorder and to attribute their illness to a physical cause.

Wood et al (1991) compared the psychiatric status of CFS patients with a muscle disease group and found that 26.5% of the CFS patients had been treated in the past, before the onset of fatigue, for a psychiatric disorder, and that 41% currently had sufficient symptoms to be regarded as suffering from a psychiatric disorder.

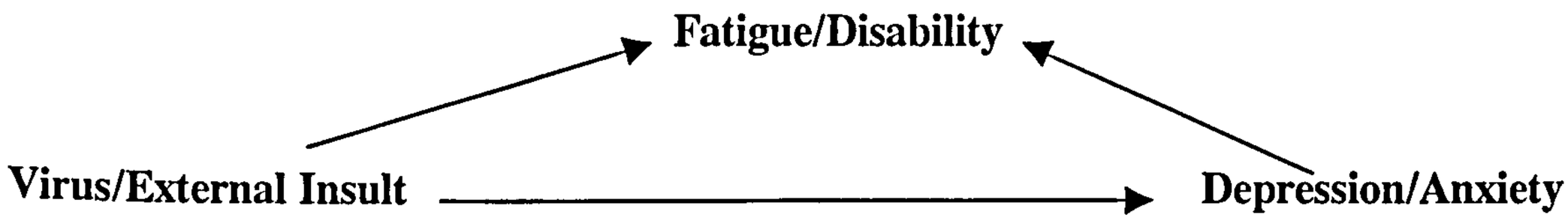
Several of the studies examining the link between psychiatric morbidity and chronic fatigue have given rise to conflicting results. Hickie et al (1990) concluded, from follow up of CFS patients, that the psychiatric illness was the consequence rather than the cause of fatigue. Conversely, Manu et al (1989) concluded, using similar diagnostic techniques, that the fatigue was caused by the psychiatric illness in two thirds of the patients. Further studies have not lead to more conclusive agreement. A more recent study of 64 CFS patients with a relatively short mean illness duration of 20 months found only a 17% prevalence rate for all

psychiatric disorders, with a current prevalence of 45%, which is comparable to other chronic medical disorders (Shanks & Ho-Yen, 1995). They concluded that CFS patients are no more prone to overt psychological illness than the general population arguing against any simple theory of psychological causation or maintenance of CFS. In his review of fatigue and chronic fatigue syndromes, White (1990), has put forward two suggestions: "(i) an independent factor predisposed some individuals to develop both depressive illness and a fatigue syndrome as a response to different physical and psychological stresses, (ii) the fatigue syndrome was the somatic presentation of a depressive illness in some patients."

A lot of the symptoms cited for CFS share considerable overlap with those of depression. However, most CFS patients claim that they are not depressed or that depression is not the key, although it may be contributory, to their problem. Long term psychological effects have been noted following infectious mononucleosis. It has been suggested that this illness can have persistent neurological and psychiatric consequences in a minority of cases, and that depression here may be organically caused and secondary to nervous system involvement (Hendler, 1987). It may also be possible that the depression in post-viral syndromes could reflect a neurochemical change induced by the virus (Sachar, 1975). The question arising from a lot of the evidence of links between CFS and psychiatric disorders is that, if a person is physically ill and depressed, their emotional state could reflect a dispositional tendency to depression, or it could represent a symptom of the illness. The depression may just be a reaction to the situation and chronicity of the illness. Indeed, in his review, Lishman (1988) suggested that "organic" factors are chiefly relevant in the earlier stages but that persistent symptoms are perpetuated by psychological factors. An interesting observation from a study by Wood et al (1991) was that those fatigue patients who reported a viral illness at the onset of their symptoms were more likely to have a psychiatric diagnosis. They also found that 32% of the fatigue patients studied reported a major, stressful life event in the six months preceding the onset of fatigue. It is perfectly plausible that the chronic fatigue syndrome would be likely to give rise to a depressive *reaction* to the impairment that is involved. However, Wessely and Powell (1989) concluded, in their study, that the psychiatric disorders in CFS patients were more than just an understandable reaction to a fatiguing illness. It must

also be remembered that not all CFS patients meet psychiatric criteria, therefore psychiatric disorders cannot be the sole explanation for CFS.

Depression does not offer a complete explanation for CFS, since it is found only in between one and two thirds of the cases (Sharpe, 1991). It is also worth noting, that there is a group making up a quarter of the samples in whom no psychiatric diagnosis was reached (Manu et al, 1988). David (1991), therefore, proposed an integrated model that is more likely to describe what actually happens in individual cases:



2.2.4 Psychological Factors

Attention has also been directed towards the role of cognitive distortions, and the ensuing maladaptive behaviour, as mediators of impairment in many illnesses, both physical and psychological. With regard to CFS, it is possible that an initial infection may then lead to the development of a cycle of attributional and cognitive factors, which can then lead to avoidant behaviour. These psychological factors (behaviour, beliefs and attitudes) will have a more important effect on how a patient copes with CFS, their rehabilitation and their expectations in the eventual outcome. Watts (1982) considered the implications of attributing illness to either psychological or organic factors, given the observation that symptoms attributed to an external cause are usually less debilitating than symptoms attributed to a personal or "internal" cause. Wessely et al (1989) have described the attributions that CFS patients make about their symptoms and their role in perpetuating disability. They discuss a state of "learned helplessness" that may follow on from the initial symptoms of fatigue and myalgia, which may become 'potent, aversive and uncontrollable'. This may also exacerbate the mood disorder that is found in many CFS patients (Wessely & Powell, 1989).

Several researchers have demonstrated a relationship between personality factors and the development of a fatigue state or an extended recovery from illness. White (1990) summarises the literature on the association between personality and fatigue states. From a study on 58 CFS patients, Blakely (1991) found that the largest subgroup was characterised by hypochondriasis/hysteria (40%). This group was over-controlled and defensive, denying psychiatric symptoms while endorsing CFS symptoms. He concluded that there was 'no unique set of psychological characteristics which can be considered as necessary antecedents or consequences of CFS', but suggested that high levels of emotionality or neuroticism may act as predisposing factors. From anecdotal observations, Abbey (1993) describes CFS sufferers as previously having highly productive lifestyles and this plays a more important part in maintaining self-esteem than in other patient groups. In this respect, they would be particularly susceptible to the psychological impact of disability, as a result of a severe or prolonged illness. Lewis (1994) confirmed that CFS sufferers rate themselves higher than controls on the "hard driving" and "many outside interests" items of the Bortner type A personality scale and they were shown to adopt a more conformational coping style. Also, van Houdehowe et al (1995) found that CFS sufferers might possess personality types more likely to generate stress than non-sufferers, being high on self-ratings on an "action proneness" scale.

Psychological factors may play a role in acquiring and recovering from infection. Cohen and colleagues from the MRC Common Cold Unit, showed that measures of psychological stress predicted infection with the common cold virus (Cohen et al, 1991). Also, a Swedish study of the outcome of aseptic meningitis, post-infectious fatigability was predicted by premorbid psychological status (Muller et al 1958). For an overview of the way in which stress may influence the onset and cause of infectious illness see White (1990a).

One important fact arising from psychological studies on CFS is that it is difficult to consider fatigue as being either organic of psychological in origin, since both factors can make contributions. Psychological factors may interact with organic factors in producing illness, thus playing a contributory role without being causally sufficient. Wessley et al (1989)

describe cognitive and behavioural factors which may lead to the development of a chronic condition from a possible organic onset. There is also evidence that psychological stress, before or at the time of infection, is a powerful predictor of fatigue persisting after viral infection (Wessely et al, 1995). Even if all cases of CFS are initially the result of viral infection, the secondary consequences, both social and psychological, may be a more potent cause of long term disability (Butler et al, 1991). Avoidance of activity and mood disorder could sustain symptoms, and create a vicious circle including expectations of failure, a belief in the continuation of the original illness, decreased physiological and psychological tolerance and feeling of helplessness and loss of control. In this case, the patients' attempts to cope with the symptoms, and subsequent avoidant behaviour, may paradoxically perpetuate the symptoms.

2.2.5 Life events / Stress

Behavioural and cognitive factors have been examined with respect to perpetuation of disability in CFS (Wessely, 1995) but less attention has been diverted to the impact of psychosocial stressors and non-pathological responses to stress in the development of CFS. A relatively small number of studies have examined the implications of stress in the aetiology of CFS, mainly in the form of life events. There has been some evidence that stressful life events and ongoing situations appraised as stressful may contribute to illness via changes in the immune system (Dorian et al, 1986) and/or through the effects on mental health (Brown & Harris, 1989). Surawy et al (1995) reported that the onset of illness occurred in association with a viral illness in 100 CFS patients interviewed, but that on further questioning, patients frequently revealed major psychosocial stressors preceding the onset of the illness. Typical examples were chronic relationship or work problems, difficulty in adapting to life changes and bereavement. Similarly, Stricklin et al (1990) reported a significantly greater severity of stress experienced in a group of 25 patients with epidemic neuoromyasthemia, compared to healthy controls in the 12 months prior to the onset of the illness, with bereavement being the most common event. They suggested that this was a psychological illness precipitated by a combination of stress and an infectious agent. Wood et al (1991), also found that 32.4% of a group of CFS patients studied, reported a major,

stressful life event in the 6 months preceding the onset of fatigue, with job changes and moving house being the most common. Conversely, Lewis et al (1994), examined life events in the two years prior to the onset of illness in CFS and irritable bowel syndrome patients and found that of 42 life events, only two, both of which were related to moving house, were more frequently reported by the CFS group. They suggested that any association between life events and illness onset may also apply to the IBS group. One difference found was that the CFS group perceived significantly less overall support prior to their illness than the IBS group and the healthy controls. They suggested that every day minor hassles may predict ill health better than major life events and that they may be more related to the onset and course of CFS. However, this has yet to be confirmed. Similarly, Bruce-Jones et al (1994) found little relationship between social adversity and the development of PIFS in a group of patients assessed at onset, two and six months after glandular fever. Surawy et al (1995) has put forward a cognitive model to describe the aetiology of CFS (Table 2.1). In this case the precipitating factors may be a combination of psychosocial stress and an acute illness.

Table 2.1. Aetiological Factors in CFS

Premorbid personality	Hard-working & achievement-orientated
	Tendency to "bottle up " feelings
Events at onset	Chronic pressures to perform
	Life events
	Symptoms of acute illness

Lewis et al (1994) also examined personality variables, in the form of type A behaviour in CFS patients and found that those individuals who were vulnerable to CFS appear to be characterised by "hard-driving behaviour and problem orientated, problem-focused coping styles", suggesting a self-induced, pressurised lifestyle prior to their illness. CFS patients in another study also talked of high achievement orientation, perfectionism, high standards of work performance with persistent striving to meet the needs and expectations of others, often at the expense of neglecting their own personal needs (Suraway et al, 1995). Indeed, several

interviewees in a qualitative study on 50 CFS patients by Ware (1993) spontaneously referred to themselves as being type A.

It must be acknowledged that these studies are, by their very nature, retrospective and recall can obviously be affected by illness, but it is also important that premorbid psychosocial stressors and personality/behaviour characteristics should not be ignored in the aetiology, and thus treatment, of CFS, particularly from the point of preventing relapse.

2.2.6 Sleep Disorders

A few studies have shown that factors that disturb sleep, such as psychological distress, noxious environmental disturbance, primary sleep disorders, or inflammatory joint disorders can contribute to a non-restorative sleep syndrome. Fragmented sleep with periodic limb movements (Moldofsky, 1984) or sleep apnoea (Molony et al, 1986) have been found in patients with fibromyalgia, which has been shown to share many symptoms with CFS (White, 1990). Many of the behavioural and somatic features associated with both fibromyalgia and CFS, such as fatigue, negative mood and impaired intellectual function, can be induced by total or partial sleep deprivation or prolonged wakefulness (Moldofsky, 1986). Other symptoms of sleep deprivation include emotional distress, progressive temporal and cognitive disorganisation, impaired performance on memory tasks and low concentration (all symptoms of CFS) can be reversed with normal slow-wave NREM sleep (Horne, 1988).

A study comparing CFS patients with normal subjects found that the patient group had more difficulty falling asleep, spent less time asleep, had reduced REM sleep and greater alpha EEG activity during NREM sleep (Whelton, 1992). Buchwald et al (1994) showed, using polysomnography, that 41% of a highly selected group of CFS patients, had abnormal results for a multiple sleep latency test and 81% had at least one sleep disorder - sleep apnoea (44%) or idiopathic hypersomnia (12%). They concluded that a potentially treatable sleep disorder may coexist with CFS. Other studies have shown that around 60% of patients with CFS also suffer from sleep disorders and that these sleep patterns differ from those seen in depressed patients (Morriss et al, 1993; Krupp et al, 1993).

Similarly, Manu et al (1994) used polysomnography with a group of 30 patients referred for evaluation of chronic fatigue. Thirty three percent had a primary sleep disorder and although alpha-delta sleep was identified in 26% of the group, this was not more closely associated with, fibromyalgia or depression.

A small amount of research has demonstrated a link between certain cytokines and aspects of cellular immune function and the sleep-wake cycle and have suggested that a disturbance in sleep-wake related immune functions may provide a link to the symptoms of CFS (Krueger et al, 1990). Further research is needed to examine a potential link between disruption in normal overnight sleep physiology and any associated alteration in immune functions in CFS. Sleep disorders are confounding factors in CFS that have not received enough attention particularly since they are potentially treatable

2.2.7 Neuroendocrine abnormalities

Hypothalamic-Pituitary-Adrenal (HPA) axis

Due to similarities in symptoms (fatigue, mood and sleep disturbance) recognised between Addison's disease, which is caused by a primary adrenal insufficiency leading to hypocortisolemia and CFS, some recent research has searched for abnormalities in the HPA axis in CFS sufferers, as a potential causative factor. Demitrack et al (1991) found a blunted adrenocorticotrophic hormone (ACTH) release in response to corticotrophin releasing hormone (CRH) in CFS patients compared to controls and a decreased 24-hour urinary total free cortisol output. These results suggest that patients with CFS have a mild form of hypocortisolism, probably due to a deficit in the hypothalamus or above. Cleare and Wessely (1996) suggest that this HPA axis perturbation and hypocortisolemia could be a final common biological pathway in the perpetuation of CFS, which could be initially be caused by a variety of physiological and physical triggers. The possibility exists that a short-lived infection, with or without the presence of psychological stress, results in a disturbance of the HPA axis, which persists long after the infection has been eliminated. This persistent dysregulation of

the HPA impacts on brain functioning. In this respect, neurotransmitter abnormalities in CFS are secondary to dysfunction of the HPA axis (National Task Force, 1994).

2.2.8 Muscle Dysfunction

At the onset of the chronic fatigue syndrome the primary symptoms tend to be those associated with viral infections, as well as headaches, dizziness and general aches and pains. A large proportion of the chronic symptoms, experienced by patients, tend to be muscular; muscle weakness and tenderness, muscle tremor, profound fatigue (muscular and mental) and extreme debility, as well as the psychological symptoms. These persistent and ongoing symptoms of weakness, fatigue and muscular pain have led researchers to examine muscle tissue and to test muscular function in the search for an underlying cause. The focus has been to determine whether the fatigue is central in origin, ie. due to a failure to recruit motor units, or peripheral, due to the failure of neuromuscular transmission, sarcolemmal excitation or excitation-contraction coupling (Edwards, 1986).

A reduction of activity of some glycolytic enzymes of skeletal muscle has been found after acute febrile infections (Astrom et al, 1976). It is logical to explore the possibility of a defect in biochemical pathways responsible for energy exchange. Of 109 patients attending a clinic dealing with muscle pain, only a small proportion exhibited an objective abnormality in the muscle (Mills & Edwards, 1983). In primary fibromyalgia, "moth-eaten " Type 1 fibres have been seen in muscle biopsies (Henrikkson et al, 1982), suggesting continuous muscle fibre activity, similar to that observed in disorders of postural muscle control. Fatigue with dynamic exercise occurs with excessive lactic acid production in patients with mitochondrial disorders (Edwards et al, 1982). Muscle pain can also be due to ultrastructural damage and associated with large increases in plasma creatine kinase activity (Henrikkson et al, 1982) In a large biopsy study on 74 CFS patients, Edwards et al (1993), found morphological abnormalities in 81% of the CFS group compared to 32% of controls. However, the clinical significance of type I fibre atrophy is uncertain and they observed no overall tendency towards fibre atrophy. Necrosis was found in both the CFS patients and the control group.

None of the abnormalities found were consistent, nor did they reach statistical significance, when the two groups were compared. They concluded that CFS is not a myopathy.

In order to examine some of the metabolic changes potentially associated with CFS, Wagenmakers et al (1988) took muscle biopsies from 23 CFS patients, 8 McArdle's disease patients and 14 untrained controls and measured the activities of mitochondrial enzymes. Cytochrome C oxidase and citrate synthetase activities were reduced to 64% and 74% of the control levels, respectively. They measured a low mitochondrial content in the majority of the CFS patients, while the 6 patients, who performed a cycling test, also exhibited a high degree of exercise stress at low intensities, decreased endurance, tachycardia and an increased dependence on glycolysis leading to a high lactate production at low exercise intensities. However, they suggested that many of the biochemical changes during exercise and many of the symptoms of these patients could be a consequence of their reduced habitual activity levels. Additionally, they maintained that the decreased levels of activity may have increased the proportion of type II muscle fibres with a low capacity for aerobic metabolism, leading to a new reduced limit to the amount of exercise that could be done without lactate production. Edwards et al (1993) suggested that although mitochondrial abnormalities have been described in CFS patients, mitochondrial function tests have been normal or may reflect the level of activity of the patients being studied.

Some later studies again used Phosphorus[31] Nuclear Magnetic Resonance Spectroscopy to examine skeletal muscle bioenergetics in CFS patients during and after exercise. Wong et al (1992) found that PCr, Pi and pH all reached peak values more rapidly in CFS patients who also had lower concentrations of ATP at fatigue, which occurred earlier, when compared to normal subjects. They suggested that this signified a defect in oxidative metabolism with a resultant acceleration of glycolysis in working skeletal muscle of CFS patients. However, Barnes et al (1993) found, in 46 CFS patients following a standard handgrip protocol, no evidence of mitochondrial defect nor a consistent abnormality in pH regulation, concluding that there was no consistent bioenergetic abnormality in CFS patients that could explain the prominent symptom of fatigue.

Byrne and Trounce (1987) used electron microscopy to examine muscle biopsy samples from CFS patients and showed no definite abnormalities in the biochemical analysis of a range of glycolytic and mitochondrial enzymes. These findings are consistent with the absence of a major deficit in intermediary energy metabolism in muscle. Evidence from unreplicated EMG studies showed increased jitter, but this could not adequately explain the symptom of excessive fatigue (Jamal and Hansen, 1985), since several sites are required to function to cause reduced motor performance, it is possible to have muscular fatigue when the muscle itself is not impaired.

One possible explanation put forward for the prolonged symptoms of excessive fatigue in CFS is the persistence of "low-frequency fatigue", which is thought to arise from a failure in excitation-contraction coupling and is associated with the need for greater central drive to overcome the likely reduction in force per impulse (Newham et al, 1983). Stokes & Young, (1984), found no evidence to support this explanation since no difference was found between CFS patients and controls in the force/frequency curve or the rate of force decline. Since neither low frequency fatigue nor failure of neuromuscular transmission (or failure of sarcolemmal excitation) could adequately explain the symptom of prolonged fatigue, Edwards et al (1993) concluded that it was not due to muscle abnormalities or muscle disease. Similarly, Kent-Braun (1993) found no evidence of excessive acidification, abnormal metabolism or increased muscular fatigue on intermittent or sustained muscle contraction tests Nor did they find evidence of abnormal muscle membrane function or excitation-contraction coupling in 7 CFS patients compared to healthy, sedentary controls. However, patients generated less force than controls and had a greater added force with tetanic stimulation, suggesting the presence of central fatigue and a possible psychological component to CFS.

Because profound muscle fatigue, precipitated by minimal physical activity, is one of the most prominent complaints amongst patients with PIFS and CFS, several studies have examined muscle performance, in an effort to determine the site of the disturbance. Muscle fatigue is defined as the loss of ability to generate force and it can be central or peripheral (Jones, 1989). Friman (1985) examined the effect of acute infectious disease on human

isometric muscle endurance (anaerobic work). Previously, he had observed reduced isometric muscle strength in patients convalescing from infectious diseases (Friman, 1978). He studied 32 male patients suffering from various acute infectious diseases. Isometric endurance was measured immediately after the fever, 1 and 4 months after, and measurements after one year were taken as control values. The subjects' endurance capacity was reduced to 82-87% of the control, and impairments were still evident at 4 months. No loss in isometric endurance capacity was observed in healthy controls confined to bed for the same period. He proposed that reduced glycolytic capacity, mediated by reduced glycolytic enzyme activity, may have been partly responsible for the reduced endurance as well as the possibility of muscle hypotrophy.

Lloyd et al (1988) measured maximal isometric strength before, during, and after a series of maximal contractions of the elbow flexors and found that the maximal isometric torque (force) was not significantly different between 20 patients with CFS compared to 20 controls. However the patients did show a significant impairment in recovery of maximal isometric strength after the endurance sequence, whereas the controls did not. They suggested that this may result from an inability to generate a maximal motor command from the central nervous system (CNS) and it is unlikely that the muscle is the major site of dysfunction in patients with CFS. Their conclusion implied that the abnormality is in the perception of muscle force and effort rather than of actual force production, that leads to the fatigue associated with CFS. However, the lack of twitch interpolation, to control for central inhibition, meant that this conclusion was uncertain.

In their later paper, Lloyd et al (1991) examined the subjective perception of effort during prolonged submaximal isometric exercise in 12 male CFS patients compared to 13 healthy controls. This type of exercise resembled the demand put on the muscle in usual daily activities. They found no significant differences between the relative torque produced by either voluntarily or electrically stimulated contractions, when comparing patients and controls throughout the test, nor did they find any significant difference in perceived exertion between the two groups. This suggested that failure of the link between motor drive and the

metabolic mechanisms of the muscle is not the site of the pathophysiology producing fatigue in CFS patients. They also refuted the significance of excessive intracellular acidosis in some CFS patients observed by Arnold et al (1984) and Yonge (1988). Arnold used Phosphorus[31] Nuclear Magnetic Resonance Spectroscopy to report an abnormal rapid decline in pH in active forearm muscle during handgrip exercise in a single patient with post-viral fatigue syndrome, but they did not control for the effects of rest. In arguing against the significance of these results, their conclusions suggested that the critical pathophysiological abnormality responsible for the prominent subjective fatigability associated with this condition must therefore lie within the central nervous system, above the level of the motor cortex. They believe that this also ties in with the prevalent psychological symptoms. Central fatigue is thought to be important in limiting activity, as signals from the skin, joint and tendon receptors feed back to the central nervous system, allowing both conscious and unconscious mechanisms in the perception of fatigue (Jones, 1989).

Further efforts to determine whether the fatigue associated with CFS was central or peripheral in origin were made by Stokes et al (1988). Central fatigue was examined by testing the exercise capacity of the whole body and the strength of the quadriceps femoris on voluntary movement, and peripheral fatigue was examined using stimulation of the adductor pollicis to test strength and fatigability in the absence of volitional control. Any abnormalities in performance occurred only during voluntary activity, whereas the contractile strength and recovery of muscle after the exercise, were both normal in the CFS patients. This suggested an impairment of central mechanisms, which could be due to a lack of motivation or fear of pain, or possibly due to a reflex inhibition by afferent activity arising from damaged painful joints (Stokes and Young, 1984). A similar technique of percutaneous stimulation was used in twitch superimposition of the quadriceps muscle by Rutherford and White (1991). They measured maximum quadriceps isometric (MVC) strength, activation and fatigability (repeated contractions at 60% MVC) in 11 fatigued patients following a corroborated viral infection and compared them with healthy controls. Two of the patients could not fully activate their muscle but allowing for this (with stimulation) the group mean strength was 104% of the predicted normal muscle strength for their height and age. There

was a remarkable trend for the patients to show less muscle fatigue than the healthy controls on the endurance test. They concluded that the feelings of fatigue and weakness by these patients could not easily be interpreted as either physiological muscle fatigue or lack of effort. However, they did acknowledge that the single limb model used in this study did not simulate normal daily movement patterns that these type of patients have difficulty with, and they may actually be limited in activities involving larger muscles, where more stress is placed on the cardiovascular and respiratory systems.

2.2.9 Cardiovascular deconditioning and physical inactivity

A few groups have examined cardiovascular and aerobic capacity in patients with PIFS or CFS. One of the earlier studies compared the exercise response between effort syndrome patients and patients with anxiety states and healthy controls on a five minute submaximal cycling test (Jones et al, 1946). The effort syndrome and anxiety states showed similar significantly higher heart rates, peak blood lactate levels and oxygen uptake values in the 5 minute post exercise period when compared to the control group. Montague et al (1989) examined resting cardiac function and exercise performance in 41 CFS patients compared with age and sex-matched controls on a supine cycle ergometer test. The CFS patients had no evidence of underlying mechanical or electrical abnormalities at rest or during 24-hour ambulatory ECG measurements. Only 13% of the CFS patients could continue the graded exercise test to the target heart rate of 85% of age-predicted maximum, compared to 63% of controls. The CFS patients stopped due to fatigue whereas the controls were more likely to stop because they had reached their target heart rate. The CFS patients terminated the test at a mean peak heart rate of 124 beats per minute whereas the mean peak heart rate reached in the control group was 152 beats per minute. There were also significant difference in test duration, with the CFS patients continuing for only 9 minutes and the control group continuing for 12 minutes. This study highlights a marked limitation in exercise capacity in this group of CFS patients but, in this case, the size of the peripheral effect appeared greater than the size of the cardiac effect. Despite a low heart rate, it is possible that the reduced aerobic capacity at the muscular level prevented continuation of the exercise test.

Another study by Riley et al (1990) compared the aerobic capacity of 13 CFS patients with that of a 13 matched normal controls and 7 irritable bowel syndrome patients. All participants performed a symptom limited Bruce walking test on the treadmill with continuous measurements of heart rate and expired air analysis. Blood samples were taken at rest, at peak exercise and during recovery and analyzed for lactate, phosphate, glucose and creatine kinase activity. The CFS patients had a reduced exercise time on the treadmill, higher heart rates and peak blood lactate levels and higher ratings of perceived exertion on the Borg scale compared to both other groups tested. The CFS patients had an altered perception of their degree of exertion and also of their premorbid level of physical activity. They concluded that there was no evidence for a deficient cardiovascular response or peripheral muscle function besides that which might be expected as a result of deconditioning. A more recent study by Gibson et al (1993) measured maximal isometric quadriceps strength at rest and following an incremental cycle test to exhaustion in twelve CFS patients and compared them to sedentary controls. No differences were found in exercise duration, heart rate/work rate relationships, or in muscle function. However, peak heart rates and blood lactates were lower in the CFS patients and they had raised perceived exertion scores during the exercise. The CFS patients showed a linear increase in effort perception with increasing intensity whereas the control subjects showed a threshold in effort perception at about 20-30% of maximum capacity followed by a linear increase. They suggested that CFS patients have a lower threshold for sensation during exercise or that they have an additional perception of fatigue at rest over and above that experienced during exercise, and they concluded that central fatigue was limiting exercise capacity in these patients. The pathological mechanism of muscle disuse and the resultant complications of weakness, atrophy and diminished endurance is most likely similar to the disuse phenomenom, which has been extensively studied and described in other groups of patients who have neuromuscular lesions and/or lead sedentary lives (Kottke, 1966).

Disuse and inactivity have a harmful effect on muscle, respiratory and cardiovascular function (Greenleaf and Kozlowski, 1982). Whether the initial cause is physical or psychological, the ensuing reduced activity level, will unavoidably lead to deconditioning. If physical conditioning is considered as general training to improve aerobic fitness, muscle

strength and endurance, then the effect of extended periods of inactivity would be expected to reverse these improvements, a deconditioning response. A mean reduction in maximum oxygen uptake of 28% was observed in 5 healthy males after 20 days of bedrest (Saltin et al, 1968). Similarly, a decrease of 15% in mean peak oxygen uptake values (25.8 to 21.9 mls.kg^{-1}.min^{-1}) was observed in sedentary individuals after only 10 days of bed rest (Hung et al, 1983). This is largely caused by the decreased cardiac output and stroke volume (29%) and left ventricular function associated with inactivity and bed rest (Taylor et al, 1949; Vetter et al, 1971). Inactivity reduces the stroke volume and perhaps the efficiency of the circulatory regulation during exercise. The margin between aerobic demands of daily activities and the maximum aerobic power becomes narrower and, sooner or later, this will create symptoms. In addition, inactivity is associated with changes in body composition in the form of increased body fat and loss of lean body mass resulting in decreased muscle strength but these effects can be counteracted through a programme of active muscle use (Deitrack et al, 1948). The slow twitch muscle fibres seem particularly sensitive to disuse and changes in their function would also be expected to result in significant reductions in stamina and capacity for physical activity. When no tension is exerted throughout the day (as in bedrest), loss of strength occurs at the rate of approximately 3% per day (Kottke, 1966).

Much of the observed low exercise tolerance in CFS patients may be a result of dramatically reduced activity levels, complete inactivity and bedrest. The resultant deconditioning in turn can lead to further avoidance of activity and further reductions in exercise tolerance.

2.2.10 Summary

The heterogeneous nature of chronic fatigue syndrome was noted by Swartz (1988), who stated that it is likely to have multiple psychosomatic and somatic causes, making the aetiology somewhat inconclusive. Several studies have identified viral triggers in CFS, with EBV, Coxsackie B and Herpes viruses all being implicated. However no one viral cause, positive in all cases, has been identified and therefore, serological tests for these viruses cannot be used as a diagnostic test for CFS. Additional infectious agents including bacteria,

parasites and other viruses have been implicated as triggering agents in CFS, although, thus far, no convincing evidence for a direct causal relationship has been established.

Links between psychological stress, physical activity, depression and the immune system have been well established (Calabrese et al, 1987; Dorian & Garfinkel, 1987), which probably explains the immune abnormalities reported in association with CFS. Some studies have found evidence of relatively minor abnormalities in a proportion of patients, but no consistent picture has been established nor has an association of immune status and clinical state been determined (Buchwald & Komoroff, 1991).

A large proportion of CFS patients meet criteria for a psychiatric diagnosis, with depression, anxiety and panic disorders being the most common. It is unresolved whether the depression is a reaction to the chronic fatigue state or whether a preceding psychiatric disorder leads to the development of CFS. Both muscle pain and fatigue are prominent symptoms of depression such that the symptoms of CFS patients are commonly difficult to distinguish from those of patients with depressive disorders (Wessely & Powell, 1989). However, since depression is only found in one to two thirds of CFS patients with one-third of CFS patients having no psychiatric diagnosis, it cannot be offered as a sole cause in all cases, and the possibility of depression as a reaction to prolonged fatigue cannot be ruled out, in some cases. Those who advocate a cognitive model in the aetiology of CFS suggest that the symptoms associated with CFS (fatigue, poor concentration, muscle pain), result from the physiological changes accompanying chronic emotional distress and inactivity, which act as a perpetuating factor (Surawy et al, 1995). Therefore, once the illness is established, cognitive, behavioural, emotional, physiological and social factors may perpetuate it, once the combination of a minor acute illness and psychosocial events act as precipitators.

It has also been suggested that psychological factors, such as cognitions, attitudes and behaviours, can interact with both physiological and psychiatric disorders to perpetuate the symptoms associated with CFS (Wessely et al, 1989). Certain personality types may be more susceptible to the development of a chronic fatigue condition, and consequent avoidant

behaviour and inactivity can lead to a vicious circle of low expectations of eventual outcome and decreased physical and psychological tolerance (Magnusson et al, in press).

The symptoms of weakness, muscle pain and disproportionate fatigue have lead researchers to examine muscle tissue and test muscle function in search of a physical explanation. No consistent metabolic or biochemical abnormalities have been discovered other than those explained as a consequence of reduced habitual activity levels (Wagenmakers et al, 1988). In exercise studies, normal muscle strength and fatigability, a decreased exercise tolerance and an altered perception of exertion have been measured (Riley et al, 1990; Rutherford & White, 1991). This has lead researchers to look away from peripheral (muscular) causes and to turn towards central impairment as a cause for the fatigue. Perhaps as a consequence of the muscle pain and weakness and fatigue, CFS patients tend to have low habitual activity levels. The detrimental effects of inactivity on muscle, cardiorespiratory function have been documented and this will undoubtedly play an important role in perpetuating the symptoms of chronic fatigue.

Laboratory abnormalities have been detected in the immune, endocrine, muscular and central nervous systems in a variable minority of patients (Blondel-Hill & Schafen, 1993). A lack of consistent or highly prevalent abnormalities is the rule. Not one but several causative factors have been proposed for CFS, some possibly precipitating and some more perpetuating in nature. There may be several causes but the search will still continue for an organic cause of fatigue that predisposes patients to psychiatric illness (Greenberg, 1990).

2.3 Treatment

2.3.1 Anti-viral

Studies on the treatment of CFS have been relatively limited to date although recommended guidelines have been prolific. A recent book devoted only six out of seventy-five chapters to treatment, all of which were studies using immunological therapeutic agents (Hyde et al, 1992).

If CFS is associated with a persistent virus, an improvement would be expected with effective anti-viral treatment. Amantadine, which is used to provide protection against Influenza A, has been reported to reduce fatigue symptoms in a placebo-controlled study of multiple sclerosis patients (Rozenberg, 1988). It would be expected that it could have a beneficial effect in CFS but no clinical trial has been conducted. Epstein Barr virus is also widely implicated in the pathogenesis of CFS, and Acyclovir, an anti-viral drug, which inhibits DNA replication, that is active against herpes viruses (including EBV), has been used in a clinical trial with no greater effects than placebo in CFS patients (Straus et al, 1988).

2.3.2 Immunotherapy

Presuming that the virus initiates an immune system response that can lead to chronic activation of the immune system, several treatments have been devised to modulate this. Some CFS patients were found to have specific Ig subclass deficiencies or a decrease in antibody-dependent cell-mediated cytotoxicity such that intravenous and intramuscular immunoglobulin was administered (Gantz & Holmes, 1989). Lloyd et al (1990) advocated the use of intravenous immunoglobulin in CFS patients following a 43% response (symptom improvement) compared to 12% on placebo in a group of 49 CFS patients, whereas Peterson et al (1990) observed no objective therapeutic advantage in immunoglobulin therapy versus placebo, in 30 CFS patients, with 25% of patients in each group reporting some improvement. Infusion of antibodies active against Coxsackie viruses, which have been described in the aetiology of CFS, using plasma exchange (to remove the circulating immune complexes) and fresh frozen plasma, produced only a mild and very temporary subjective improvement (Behan & Behan, 1988). No evidence of improvement was observed using immune system stimulants such as, interferon, interleukin-2, transfer factor or immunovir which was also the case with immunosuppressive treatment (Behan & Behan, 1988). There also appears to be no advantage from treatmemt with thymic hormones (to stimulate T cell production) or inosine probanex/Immunovir (a drug also having weak anti-viral properties) (National Task Force, 19944). Although the role of immunoglobulins has not been resolved,

the current recommendations, based on expense, tolerability and available efficacy data, is that its use in CFS is not routinely justified (Straus, 1990).

2.3.3 Essential fatty acids

Behan et al (1990a) has proposed that the post viral fatigue syndrome is triggered by the effects of a viral infection on essential fatty acid (EFA) metabolism, leading to a general reduction in EFA levels, making it more difficult for the host to eliminate viruses, an increased risk of ongoing infection and persistence of the syndrome. In a 3 month, placebo controlled trial, 85% of PVFS patients on Efamol Marine, a combination of 80% evening primrose oil and 20% fish oil, rated themselves better than baseline compared to 17% of the placebo. Behan et al (1990b) reported a 74% improvement over baseline after one month of Efamol marine treatment compared to 23% of controls, with significant changes in essential fatty acid levels measured in the red cell membrane phospholipids. However, the results of these studies have not been replicated and an unpublished, 6-month randomised, double-blind trial of Efamol Marine in 98 CFS patients failed to show any difference in symptom rating between the treated and placebo group (Riley et al, 1993).

2.3.4 Sleep disturbance

Sleep disturbance is also a common symptom of CFS, and several neurotransmitters are involved in the regulation of sleep, including serotonin, acetylcholine, gamma-aminobutyric acid and catecholamines (Jouvet at al, 1983) some treatment has focused on regulation of this symptom. Conventional drugs used in the treatment of sleep disorders, such as benzodiazepines, do not appear to correct the sleep abnormalities in CFS (McClusky, 1993). However, Goldenberg et al (1986) have had some success with tricyclic antidepressants such as amitriptyline or imipramine, acting as sleep modulators in fibromyalgia patients.

2.3.5 Neurally mediated hypotension

A recent study found evidence of neurally mediated postural hypotension (assessed as an abnormal response to an upright tilt test) in 22 out of 23 selected CFS patients compared to 4

out of 14 controls (Bou-Holaigah et al, 1995). Following therapy to increase the blood volume through increased dietary sodium or fludrocortisone, 9 patients reported complete or near complete resolution of CFS symptoms. These patients were selected and the treatment was open, without a placebo comparison.

2.3.6 Neuroendocrine

If hypocortisolemia is of causal importance in some or all of the symptoms of CFS, then treatment with hydrocortisone therapy could be of benefit. This hypothesis is currently being examined by a double-blind, placebo-controlled trial (Cleare & Wessely, 1995).

2.3.7 Psychiatric and Psychological

Most other studies have approached the treatment from the psychiatric or psychological aspect. Whether the cause or the consequence of CFS, an emotional disorder can be a source of fatigue and disability (Wessely & Powell, 1989), but it can be effectively treated, both pharmacologically, or with cognitive behavioural therapy (CBT) (Hawton, 1989). CBT focuses on the theory that the disability seen in CFS patients is aggravated by cognitive distortions and is perpetuated by maladaptive behaviour. Butler et al (1991) observed a clinically significant improvement in symptoms and functioning, using CBT, in 69% of a group of 50 severely disabled CFS patients and this was maintained at follow-up. Cox and Findley, (1994) used a combination of CBT and occupational therapy in a pilot study with a group of 28 CFS in-patients and observed 57% of the patients had an improved activity level six months following discharge. Patients in both of these studies were also offered traditional antidepressant therapy. A more recent study compared CBT to normal medical care and found a 60% patient rated improvement compared to 23% of controls with subsequent improvement in daily function and Karnofsky score, one year after starting treatment (Sharpe et al, 1995).

Pharmacological approaches have included the use of antidepressants. Tricyclic anti-depressants have been shown to be beneficial in a controlled trial of fibromyalgia, which is closely associated with fatigue (Goldenberg, 1986). Vercoulen (1996) carried out a

randomised controlled trial of fluoxetine, known to have fewer sedative and autonomic nervous system effects than tricyclics. After 8 weeks of treatment, a 20mg daily dose of fluoxetine was found to have no superior effects to placebo on any symptoms characteristic of CFS. There is little evidence from controlled trials on anti-depressants as a treatment for CFS and one study reported that only 4 out out 55 patients felt "greatly improved", while 13 stated that they had been "made worse" (Sharpe et al, 1992).

2.3.8. Exercise and activity

Only a few studies have attempted to treat the effects of deconditioning and inactivity in CFS. This may be due, in part, to the lack of agreement on the physical aetiology of the syndrome, as well as the resurgence of symptoms observed after activity in these patients, so that those dealing with this particular group may have found it 'safer' and less contradictory to recommend rest and relaxation. Rest has commonly been the mainstay of this treatment, with work and physical activity approached with caution (Archer, 1987). Patients are frequently told to rest until symptoms subside or to modify their lifestyle and live within their own individual limits (Dowsett et al, 1990).

However, it is well documented that exercise has beneficial effects, both physically and mentally for healthy individuals (Eiseman, 1985), and also several studies have indicated that exercise may be useful as an antidepressant (Doyne et al, 1983, Martinsen, 1990). Conversely, it has also been shown that inactivity can have adverse psychological effects (Baekeland, 1970). Various community and clinical studies have indicated that individuals from a range of age groups with physical disorders, who are completely inactive, are at a greater risk of psychiatric disorder than are healthy ones (Weyerer, 1990). Patients who feel chronically fatigued and lethargic, but who do not show any signs of depression should, likewise, benefit significantly from an exercise programme (Taylor, 1985). Sheehan (1989), describes the human body as a complex machine whose proper maintenance requires regular exercise, and referred to such chronically fatigued patients as exhibiting an "exercise deficiency".

Edwards and colleagues have demonstrated the benefit and objective improvement with physical fitness training, on an individual basis, in an open, uncontrolled study of patients with "effort syndrome" (Newham and Edwards, 1979). They describe both progressive (beginning from a supine position) and constant work rate test on a cycle ergometer, with measurements of heart rate, blood pressure, power output and blood samples taken at regular intervals. The exercise programme consisted of two to four half hour cycle ergometer sessions per week, aiming at a daily progression. Supplementary exercises were also included. On repetition of the same exercise test one or two weeks later, patients already showed lower exercise and recovery heart rates, lower blood pressure and an increased work capacity. Graded exercise would seem to be a logical approach to the treatment of CFS and could rarely be contra-indicated in most disease populations. However, several current reviews on CFS do not mention exercise, possibly since it is not considered to have a curative effect (Gantz & Holmes, 1989; Blondell-Hill & Shafran, 1993). Gantz and Holmes do recommend moderate exercise to maintain muscle tone and endurance, primarily to counteract the effects of inactivity. However, they caution against excessive exercise, commenting that this may result in exacerbation of symptoms. A review by Sisto (1993), does mention that exercise programmes can help CFS, but only by giving patients a sense of control over their condition.

McCain et al (1988) has shown improvement in subjective measurements of pain with a 20 week cardiovascular fitness training programme in patients with fibrositis/fibromyalgia syndrome. Thirty-four patients were assigned to either heart-rate elevated training on the cycle-ergometer, three times per week, or a programme of flexibility only exercises. As well as improvements in myalgia, the exercise group showed a significant increase in peak work capacity, and neither of these improvements were observed in the group doing flexibility work only. Similarly, Mengshoel et al (1992) reported reduced feelings of muscular tension and an improved general feeling of well-being with a programme of low-intensity dynamic endurance training in fibromyalgia patients. A group of 18 patients formed a training group that did two one-hour aerobic exercise sessions per week for twenty weeks. The group improved their upper-extremity dynamic endurance capacity and showed a reduction in

exercise induced pain that was not seen in the control group who did not change their exercise habits for the duration.

Fatigue is a multifactorial problem with contributory causes in the areas of physiology, biochemistry, psychology and environmental sciences and therefore, improvement in several factors could decrease the liability to fatigue (Shepherd, 1974).

2.4 Benefits/Effects of Exercise

2.4.1 Psychological effects of exercise

Depressed patients tend to be inactive and have a low physical working capacity compared to non-psychiatric controls (Eisemann, 1985; Aaoro & Brekke, 1983). The few studies that have used exercise intervention in the treatment of depressed patients have given positive results (Martinsen, 1990). One of the earlier studies compared the effects of ten weeks of psychotherapy and ten weeks of running, three times per week and found that the runners has at least as much improvement as the other treatment group on SLC-90 depression scores (Greist et al, 1979). Other studies reported that, compared to either no treatment or relaxation training, aerobic exercise produced significant reductions in depression scores (Doyne et al, 1983; McCann & Holmes, 1984). Klein et al (1985) found 12 weeks of either running, meditation or psychotherapy to be equally effective in reducing depression. Other studies compared a combination of exercise plus counselling, with either treatment given alone and achieved the most significant reductions in depression scores as a result of the combination treatment (Reuter et al, 1982; Asberg et al, 1978). Freemont (1983) expanded on Reuter's study and compared cognitive therapy, running and a combination of both, and found that all treatments had equal effects on Beck depression inventory (BDI) scores. Aerobic exercise seemed to be more effective than no treatment, but was not significantly different from other forms of exercise treatment, and a combination treatment was most effective. Exercise programmes have also been associated with significant increases in self-esteem, particularly with those patients who are initially low in self esteem (Sonstroem, 1984).

With regard to the type or intensity of the exercise, Sexton et al (1989), found walking and jogging programmes to be equally effective in relieving depressive symptoms and state anxiety. They suggested that "regular light or self-selected exercise, 30 minutes three times per week" is adequate for benefit and resulted in a minimal dropout. Moses et al (1989) also reported that moderate exercise is preferable to higher intensity exercise in reducing tension-anxiety and that psychological benefits may not be directly related to improvements in maximal aerobic capacity. Lower levels of exercise may have greater psychological effects by avoiding the potentially negative effects of demanding exercise and a higher drop-out. Mutrie (1986) compared the effects of eight weeks of aerobic exercise, strengthening and stretching exercise and being on a waiting list. After four weeks, those in the aerobic group had reduced BDI scores, whereas the strengthening and stretching group and the control group showed no reduction. After eight weeks both exercise groups had decreased depression, more positive moods and were physically fitter.

It appears to be the participation in the exercise itself, rather than any improvements in physical fitness, that lead to psychological gains, as both aerobic and anaerobic exercise have shown similar effects with and without increases in functional capacity. Patients themselves evaluated physical fitness training as the most important element in the comprehensive treatment programmes (Martinsen and Medhus, 1989). By placing more emphasis on the physical side of their treatment, patients might be taking the focus away from the stigmatized psychological aspect of their illness. Additionally, it could be that the social environment may be as important on psychological outcome as the activity itself. Exercise could also provide a distraction that could, in turn, reduce state anxiety (Morgan, 1985). It is, as yet, unclear how the exercise mediates these effects. Some studies suggest that this antidepressant effect may result from the release of an endogenous endorphin, which has known analgesic and euphoric effects similar to morphine (Cronan & Howley, 1984). Other suggestions are that the exercise leads to an increase in the concentrations of monoamines in the brain (Ransford, 1982), or that it may be due to the reduced catecholamine levels after exercise (Cousineau, 1977). Since increases in serotonin (5-HT) levels in the brain can result in fatigue and sleepfulness, an increase in the concentration of 5-HT in certain areas of the brain

might be associated with a high rate of neuronal firing, which could then increase the sensitivity to fatigue (Newsholme & Castell, 1996). It is also possible that regular exercise could decrease the sensitivity of the 5-HT receptors. DeVries (1981) reported reduced EMG recordings of muscle tension after exercise, which may indicate a mechanism for reported decreases in anxiety and tension levels after exercise. Increased capacity for work may also assist the individual in coping with stress (Schafer, 1978). It could also be a combination of several of these or even other factors that mediates the psychological benefits associated with the exercise training.

The corollary of this is that inactivity has detrimental psychological effects, with the immediate emotional response to limitation of activity being similar to that in other situations of stress (Kottke, 1966). Anxiety, hostility, tension, complaints of discomfort and changes in pattern of sleep may all occur to varying degrees as a response to inactivity, depending on the individual's personality.

2.4.2 Physiological effects

Exercise has been shown to have numerous benefits, including increased longevity, and a number of profound physical changes. Aerobic exercise is associated with increased stamina and endurance, usually associated with an increased maximum aerobic capacity (VO_2 max), and a greater cardiovascular efficiency, leading to a reduced heart rate at a given oxygen uptake (Astrand & Rodahl, 1986). Subsequently, improvements in aerobic fitness lead to a decreased risk of all causes of mortality. The other well-documented effects of exercise include increased high density lipoprotein levels (Wood, 1985), increased vagal tone, stroke volume, cardiac output and blood pressure at submaximal exercise intensities (Seals et al,1984), all of which contribute to a decreased risk of heart disease (Haskell, 1984; Pate et al, 1995)

Regular exercise also increases insulin sensitivity, myocardial hypertrophy, blood volume and haemoglobin levels, but decreases platelet aggregation. At the muscular level, increased capillarisation and number and density of mitochondria lead to increased removal of the by-

products of exercise, particularly lactic acid, from the tissues and a reduced lactate production at a given exercise intensity (Astrand & Rodahl, 1986). Improved fitness also leads to a more efficient fuel usage, conserving the body's more limited glycogen reserved by using increased ability to use fatty acids as a fuel (gluconeogenesis)(Saltin et al, 1983).

Exercise also leads to an increase in the metabolic rate both during and after the exercise bout and a general increase in energy levels (Astrand & Rodahl, 1986).

Several chronic medical, conditions involve considerable bedrest and inactivity, whether during the rehabilitation from a condition or as a consequence of a long-term illness. Exercise therapy has been increasingly advocated for treatment of several chronic diseases, such as coronary artery disease, peripheral vascular disease, chronic obstructive pulmonary disease, rheumatoid arthritis, osteoporosis and chronic pain syndroms. It has been postulated that physical activity would stimulate the formation of collateral vessels, reduce the pain of claudication and increase exercise tolerance in patients with peripheral vascular disease (PVD)(Ekroth et al, 1978). After a training programme of 3 x 30 minute walking sessions per week and a general increase in daily activity for 4 to 6 months, 40% of patients with PVD could walk continuously for more than 1 kilometre, an increase of 234%. Another group reported results suggest increased peripheral blood flow following exercise training, in which maximal walking time and time to claudication pain increased (Skinner & Strandness, 1967). A recent prospective randomized controlled trial of patients with chronic obstructive pulmonary disease compared rehabilitation in the form of a package of breathing and joint mobility exercises, interval training, treadmill walking, upper body exercises, using both supervised and at home routines, with conventional community care (Goldstein et al, 1994). The treatment group improved their physiological fitness (6-minute walk distance and submaximal cycle time) and both emotional function and dyspnoea index after 24 weeks.

Patients with rheumatoid arthritis have also been reported to benefit from an exercise programme consisting of 1 hour of supervised aerobic exercise every second week and recommendations for home exercise on a bicycle ergometer (Nordemer et al, 1981). At the

completion of the study, the treatment group were 3 times more physically active than the control group, had less joint stiffness, received fewer intra-articular joint injections and oral steroids, and spent less days in hospital. Preliminary work with cystic fibrosis patients suggests that exercise may improve respiratory functions and physical work capacity (Zach et al, 1982), while in a group of post-polio patients with apparent disuse weakness, several showed significant improvements in strength in response to a carefully supervised exercise programme (Feldman, 1993). In patients with osteoporosis, although high intensity physical activity can cause fractures, walking, mobility exercises and certain other low-level exercises have been shown to prevent bone mineral loss and increase bone density (Smith et al, 1981). The ultimate goal of exercise conditioning of patients with coronary artery disease (CAD) is to increase life expectancy and to increase the quality of life through increased physical work capacity and decreased depression and anxiety. A review by Shepherd (1983) concluded that subjects allocated to exercise programmes had a 25 to 35% mortality advantage over those in control groups.

The exercise prescription, with respect to frequency, duration and intensity varies considerably in all studies with the chronically ill, depending on the level of disability. Previous guidelines by the American College of Sports Medicine (1978) "for developing and maintaining cardiorespiratory fitness and body composition in healthy adults" recommended 15-60 minutes of exercise, 3 - 5 days per week at 50 - 85% of maximum oxygen uptake. While these guidelines were meant for healthy adults, they formed the basis of exercise prescription for coronary rehabilitation, initially, and several other conditions. These guidelines have been revised taking into account that the quantity and quality of exercise needed to obtain health-related benefits may differ from what is needed for fitness benefits (ACSM, 1990). It may be more important to promote an increase in activity volume (duration and frequency) at a moderate intensity than to increase intensity above a moderate level (relative to a person's capacity (Haskell, 1994). This provides support for the value of low to moderately intense activity, especially for the chronically sedentary, overweight individuals, other patients and the elderly. The new guidelines also imply that performance of a number of short bouts of activity throughout the day, if they total 30 minutes or longer, will provide

significant health benefits, and this type of approach can be far more manageable for such individuals.

2.5 Tests for assessment of Physiological Capacity

There are many ways to assess the different aspects of fitness, and the methods chosen need to reflect the reason for undertaking the assessment. Tests on elderly, ill or disabled individuals should be more related to those factors that are important for health, well-being and independence.

The purpose of exercise testing is to determine whether there is a normal response to the challenge of continuous exercise. Clinical applications may include diagnostic, functional and therapeutic objectives. Functional exercise testing is used to determine exercise capacity. It provides information on an individual's current physical condition which can then be used to set appropriate training loads, as well as providing initial data for comparison, so that the effects of an exercise programme can be monitored. Improvements can be measured quantitatively, while also giving feedback and motivation to the patient. Because of the diversity of symptoms associated with CFS, the initial assessment of functional capacity needs to include both aerobic capacity, since CFS patients complain of abnormal fatigue during and after exercise, and muscle strength since they also complain of muscle weakness. In addition, other measures pertinent to good health should be included in order to obtain a more comprehensive assessment of the patients overall general health.

2.5.1 Measurement of aerobic fitness

Aerobic fitness is associated with a person's capacity to undertake prolonged forms of activity, ranging from daily tasks such as walking, cleaning and shopping to other more obvious forms of physical exercise. A clear link has been established between the enhancement of an individual's aerobic capacity and their ability to cope with the demands of their lifestyle (Bird, 1993).

An individuals aerobic capacity is dependent on several inter-related factors, the most important of which is the efficiency with which they utilize oxygen. A clear link exists between oxygen consumption and cardiorespiratory fitness, since oxygen delivery to tissue is dependent on lung and heart function. The maximum oxygen uptake (VO_2 Max) is the maximum rate at which oxygen can be taken in, distributed and used by the body in the performance of work. This maximum rate represents an individual's physiological limit and the VO_2 max represents the single most commonly used indicator of an individual's capacity for oxidative metabolism and exercise capacity. VO_2 max is related to heart rate through the Fick equation and is a product of maximum cardiac output and the maximal systemic arteriovenous oxygen difference, such that a linear relationship exists between heart rate and oxygen use during exercise (Astrand & Rodahl, 1986). Normally, as the work rate or intensity increases, the rate of oxygen uptake and the heart rate increase up to a plateau, after which further increases in work rate show no further increases in VO_2. In older, sedentary individuals, VO2 commonly does not reach a plateau because of a limiting symptom or sign that causes a person to cease exercise before reaching it, such as fatigue, blurred vision or angina. In this instance, the peak VO_2 measurement represents a limiting condition rather than a physiological limit. This determination is often referred to as a symptom-limited VO_2 max or functional capacity. Aerobic capacity, measured before and after an exercise programme is one of the best methods for assessing physical fitness improvement (Karlsson et al, 1967), although the use of a single measure to describe the level of physical and physiological fitness has been criticized (Ricci, 1967). For this reason, several additional measures should be made, when possible. Various factors can limit VO_2 max and these can vary in different individuals and may well be different in CFS patients compared to healthy individuals. Also, the limiting factors may change for any given individual as a result of an exercise training programme, or the onset of disease (McCully, 1993). Determination of peak VO_2 represents a relatively simple and practical means of measuring general exercise capacity and assessing the results of intervention in patients with CFS. The extensive published information on human oxidative capacity provides a broad frame of reference for interpreting results and treatment strategies.

2.5.2 Blood lactate and exercise

Energy sources in the muscle vary as exercise intensity increases. The ventilatory response reflects both changes in the substrates used and the amount of aerobic and anaerobic metabolism. During low intensity activity, free fatty acids are oxidised aerobically as the primary source of fuel. As the level of exertion increases, more carbohydrates are metabolized, as aerobic processes can no longer meet the demand for oxygen, resulting in lactate production and accumulation. Increased capacity for lactate clearance in trained individuals prevents, or minimizes lactate accumulation and lactic acidosis at higher exercise intensities. After maximal exercise, or exercise to an individual's perceived maximum level, at which stage the glycolytic processes will be the sole fuel source, blood lactate continues to rise, reaching a peak 3 to 5 minutes after exercise cessation. An accumulation of protons can be the factor that causes fatigue and will thus be a contributing factor in termination of an exercise test (Astrand & Rodahl, 1986). There is good evidence that a muscle lactic acidosis which causes intramuscular pH to decline to approximately 6.4, will interfere with excitation-contraction coupling and lead to muscle fatigue in strenuous exercise (Brooks, 1987). An individual's ability to tolerate the rising blood lactate concentration will influence the duration of exercise and their capacity to continue exercise during a maximum aerobic capacity test.

Measurement of peak blood lactate levels following a maximal exercise test will give a good indication of individual tolerance levels. The peak level of lactate will reflects the individual's "pain" threshold and therefore, their motivation to continue. Since regular exercise improves the metabolic efficiency of the muscles, having a glycogen sparing effect, blood lactate levels at submaximal workloads will also decrease and measurement of blood lactate levels before and after training provides a basis for comparison of exercise capacity and lactate tolerance. This reduced lactate accumulation that is associated with regular aerobic exercise occurs through decreased production (Holloszy & Coyle, 1984), increased clearance (Donovan & Brooks, 1983) and increased intramuscular buffering capacity (Parkhouse & McKenzie, 1984). Conversely, a lactacidosis occurs at low workloads in unfit individuals and has also been shown in patients with "vasoregulatory asthenia" (Jones et al, 1975).

2.5.3 Perceived exertion rating

It has been shown that the heart rate is linearly related to exercise intensity and can be used as a predictor of aerobic capacity (Astrand & Rhyming, 1954). The subjective rating of the intensity of exertion has also been shown to be a good indicator of the physiological work being done (Borg, 1970). The scale that was developed, based on this relationship, shows correlations of between 0.77 and 0.9 between heart rate, physiological indicators of fatigue such as oxygen consumption, blood lactate and ventilation, and a subjective rating of perceived exertion (RPE) (Pandolf, 1983). Borg's original 15 point RPE scale, has values ranging from 6 to 20, with verbal anchors at each odd integer ranging from "very, very light" to "very, very hard" (Borg, 1970). It is intended to correspond to each individual's mental tabulations of his/her own individual physiological responses

Many factors, such as pain threshold, individual sensory acuteness, experience of the activity and the overall level of conditioning affect the individual's estimate of their effort expenditure (Carlton & Rhodes, 1985). It is dependent on both central and peripheral contributions and the size of the muscle mass involved. During low intensity exercise, the physical strain in the working muscles is the primary stimulus for effort perception, while at higher intensities, above a critical threshold, the central input also contributes to effort perception (Robertson et al, 1979). Eston et al (1987), concluded that RPE was a good predictor of metabolic demand during exercise. Generally, it is agreed that local factors (blood lactate levels and muscular strain) dominate the individual's perception of exertion (Mihevic, 1981; Pandolf, 1983), particularly at low to moderate intensities. Central factors (ie. heart rate, oxygen uptake, ventilation) may serve as amplifiers to local factors relative to aerobic demand (Caferelli, 1977; Robertson, 1982). This implies that central factors would mainly dominate at higher intensities; ie. unless a physiological response is highly activated and provides input for conscious awareness, it is unlikely to have a significant impact as a perceptual cue.

Since it is well documented that the metabolic cost of submaximal exercise is reduced following an aerobic training programme (Kilbom, 1971), it would be expected that this should be perceived as involving less effort; ie. at any given submaximal workload, RPE

should be reduced following physical conditioning (Carlton & Rhodes, 1985). Ekblom and Goldbarg (1971), recorded decrements in RPE after six weeks of aerobic training in a group of rheumatoid arthritis patients and Kilbom (1971) also showed reduced submaximal RPE levels after seven weeks of bicycle training at 70%VO_2 max. Similarly, Hagberg et al (1989) found that endurance training reduced RPE for a given percentage of maximum oxygen consumption for a sample of individuals aged 70 to 79 years, whereas resistance training had no effect.

Evidence suggests that rather than a single primary cue, multiple sensory inputs of local and central origin are integrated and weighted by the individual to arrive at an evaluation of overall perceived exertion. Therefore, the use of the RPE scale in conjunction with other measures of physical fitness provides a link between physiological indicators of stress (heart rate) and a psychological indicator (subjective perception of bodily sensations), which can also be used as a measure of adaptation to training.

2.5.4 Strength measurement

In order to carry out normal daily activities successfully, muscles must possess an adequate degree of strength, a lack of which may reduce the individual's physical capacity to perform specific movements and limit the ability to undertake certain physical tasks. It is related to other aspects of an individual's capacity, and should not be considered as an isolated component. Muscle strength can be discussed in terms of a continuum from maximal strength to strength endurance and local muscle endurance. The maximal strength refers to the maximum amount of force that a muscle or group of muscles can generate in a single maximal contraction. This may determine whether they are capable of lifting or moving a heavy object. The ability to repeat or sustain muscular contractions over a set period will affect an individual's ability to carry out normal activities such as walking, carrying objects or climbing stairs. The strength of a muscle can be determined by using various types of muscular contraction. Muscle strength can be measured isometrically, isotonically or isokinetically, each of which has inherent limitations but also specific uses. It is well

documented that muscle strength decreases with age, but it has also been difficult to disentangle the effects of ageing from the decreased physical capacity that accompanies it (Bassey, 1978).

The maximum voluntary isometric force of the quadriceps is a measurement commonly made in both in clinical and experimental studies (Rutherford et al, 1986; Edwards et al, 1977). Testing of maximal strength requires a high level of motivation in the subject, which may be inhibited by fear of pain or pain itself. As a result, weakness and low recorded strength values can be due to submaximal activation of the muscle rather than muscle atrophy (Rutherford & White, 1991), due to an inherent inhibition of the expression of maximal muscular strength in humans. Also, low frequency fatigue can be attributed to impaired excitation-contraction coupling, whereby the action potential fails to release the normal amount of calcium such that fewer cross-bridges are available for force generation. To produce a maximum contraction, a high stimulation rate and a high ATP turnover are essential. Therefore, central inhibition, neuromuscular junction failure and impaired excitation of the sarcolemma, could result in reduced muscle performance (Edwards, 1982). Whether inactivity results in decreased activity of the sarcolemma, through alteration in calcium release or ATP turnover remains to be shown. In this respect muscle weakness can occur in the presence of normal muscle mass, if the patient has impaired central activation or neuromuscular transmission. The causes of fatigue are therefore regarded as being located centrally or peripherally. A technique has been developed, for use in the clinical situation, that can be used to distinguish between central and peripheral causes of weakness (Edwards et al, 1977; Rutherford & Newham, 1986). This technique involves percutaneous electrical stimulation of the quadriceps during maximal voluntary isometric contraction and is useful for identifying inhibition in the absence of pain or an inability to fully activate the muscle.

2.5.5 Resting lung function

Pulmonary function testing can exclude or confirm a suspected disorder or assist in quantifying the respiratory impairment. Resting lung function tests were included to determine that patients and subject had no underlying airways obstructions that might impair

their exercise response. The forced Vital Capacity (FVC) represents the maximal amount of gas that can be expelled from the lungs following a maximal inspiration and measures restrictive lung problems. Forced Expired Volume in 1 second (FEV1) is useful in determining if there is any airways obstruction. The maximal flow rate is limited by the rate by which the respiratory muscles are able to transform chemical energy into mechanical energy and also by a rising flow resistance.

2.5.6 Body fat percentage

Body composition is a better guide for determining the desirable body weight than the standard height-weight-age tables. Changes in activity patterns and diet, such as the changes associated with chronic illness, can have a profound effect on an individual's body composition. In this respect, prolonged inactivity can lead to large decreases in lean muscle tissues with or without gains in body fat levels, leading to loss of muscle strength and ability. A high level of body fat increases the energy demand of normal activities such that overweight individuals find it increasingly difficult to remain active. Measurement of body fat levels can, therefore, give an indication of body composition outside the desirable ranges for healthy individuals. Body fat was assessed to determine if, potentially as a result of their altered and inactive lifestyles, CFS patients had body fat levels outside or above desirable levels. It would also be possible to measure whether this changed at all during the course of the study as a result of increased activity levels.

2.6 Psychological Assessment

Accurate definition and measurement is also essential in psychological medicine, although this task is somewhat more difficult than in physical medicine. The instruments available consist of a range of validated, condition or disease specific questionnaires, rating scales and structured interviews. The development and refinement of these questionnaires, whereby patients themselves assess their symptoms, is leading to the increasing use of such instruments. For any psychiatric assessment, reliability is essential. This signifies that the

various items should demonstrate a reasonable degree of internal consistency. As a rule, a phenomenon is measured by a minimum of 6 items. The psychiatric evidence of the reliability of the scale (internal consistency) is often expressed by a correlation coefficient, wgich indicates the degree to which the selected items are positively correlated.

Two main type of scales are used in psychiatric measurement:

1. Likert scales consist of a number of categories (symptoms), each of which is rated in terms of severity, often on a five-point scale (0-4) (Likert, 1952). in this type each item on a symptom scale is characterized by means of a "quantitative" scale, e.g. 0 = not present, 1 = questionably or slightly present, 2 = present to a mild/moderate degree, 3 present to a moderate/marked degree and 4 = present to a marked/extreme degree.

2. Visual analogue scales (VAS) combine a straight line, usually 10cm in length, with verbal cues, whose two end points represent the extremes of the scale, e.g. "definitely not present" and "present to an extreme degree". The rater/patient places a mark on the line to indicate where they lie on the dimension of severity at that moment. The rating score is then the distance measured from the left extreme (not present) to the marked point, in millimeters. Some statisticians claim that the use of VAS is preferable to the categorizing scales, since they provide more complete information since, by use of a limited number of response categories, some information is lost (McCormack et al, 1988).

Questionnaire formats may vary from single-item questions, to batteries of questions, to complete summative scales. These will incorporate the response formats described above.

2.6.1 Self-report scales in psychological assessment

For the purpose of any study measuring quality of life among patients as an outcome measure of treatment provided, a decision must be made on whether to use a diagnostic screening tool or a self-report symptom questionnaire or a combination of both. Psychiatric screening

instruments can be used to provide a categorical psychiatric diagnosis, whereas self-report questionnaires yield mainly dimensional data. For assessment of health outcomes, self-reported feelings (e.g. anxiety and depression) and self-reported and observed role functioning and behaviour are sufficient indices of psychological morbidity and severity. With self-rating scales, the patient is allowed to make their own judgement of severity, using phrases like "a little" or "a great deal" because self-rating scales have to speak the patient's own language as a priority and most patients have their own lay experience on which to base their judgement. In this way a specific psychiatric screening tool may be used to diagnose and thus to highlight any conditions that would exclude a patient from entering a specific treatment programme. Self-report symptom functioning and behaviour scales will then be useful to measure change as a result of treatment. To be used in this context, a scale must have validity in terms of criterion, concurrent or predictive aspects, in that it measures what it is supposed to be measuring. Criterion validity implies that there is agreement between the scale scores and some external criterion - usually done by testing a scale against expert clinicians global judgements of severity as recorded on a numerical scale varying from 3 - 11 observations. For concurrent validity, the scale is tested against already established instruments. Predictive validity defines that the scale is designed to predict the outcome of a particular treatment. All of the rating scales used in this study have been chosen to be valid measures for the particular aspect being assessed.

A very wide range of self-report scales exists for the measurement of psychiatric and psychological variables. In addition to the more obvious symptoms of physical and mental fatigue, CFS has been linked with depression, sleep disorders and general feelings of poor health and vitality. Appropriate self-rating scales must be selected to measure changes in these parameters over time and a number of scales that have previously been employed in studies with CFS patients. Some rating scales are designed to measure changes in symptoms, whereas others focus on long-term trend. The most important function of symptom scales is that of measuring changes in symptoms over the course of the treatment period. By using the same scale before and after treatment, the effect of the individual's symptoms can be evaluated separately. When assessing emotional status, it should be noted that most scales

employed for this include symptoms that can be a manifestation of physical illness (National Task Force, 1994). The Hospital anxiety and depression scale was specifically designed to avoid such symptoms. It is a validated scale that measures both anxiety and depression in patients who have physical diseases, in order to bypass the confounding effects of mood disturbance on physical symptoms, for example, sleep disturbance, weight loss and energy levels (Zigmond & Snaith, 1983). The Pittsburgh sleep quality index (PSQI), a validated scale to measure symptomatic sleep disturbance (Buysse et al, 1988). This is a useful measure in CFS patients since sleep deprivation has been shown to have a detrimental effect on perceived exertion levels during submaximal activities (Myles, 1985). The MOS-36 (SF36) is a short form from the Medical Outcomes Studies Measures, and comprises brief scales for physical functioning, role limitations due to physical problems, role limitations due to emotional problems, social functioning, bodily pain, general mental health, vitality and general health perception (Ware & Sherbourne, 1992). A number of scales designed to assess fatigue have been developed. The visual analogue fatigue scale has been validated as a measure of both physical and mental fatigue in patients suffering from post-infectious fatigue syndromes (White et al, 1995). The Wessley fatigue scale has been validated as a measure of global subjective fatigue in patients with CFS (Chalder et al, 1993), and the Barsky scale has been validated as a measure of somatic symptoms amplification in various patient populations (Barsky et al, 1988). The clinical global impression scale is a valid and reliable scale , and has been used in the area of psychopharmacology, to measure overall change in conditions and symptoms (Guy, 1976).

CHAPTER THREE: METHODOLOGY

3.1 Screening

Ethical approval was obtained from the District (East London and the City) Health Authority Research Ethics Committee. Test procedures and all requirements of involvement were explained in detail to each patient by the senior physiologist and a qualified psychiatrist. Patients were then asked to carefully read through and sign the consent form (Appendix B).

Chronic Fatigue Syndrome subjects

Only those chronic fatigue syndrome patients fulfilling the Oxford criteria (Table 3.1) were eligible to take part (Sharpe et al, 1991). Full physical screening was carried out or, where appropriate, full recent records were obtained from the referring doctor. The purpose of this was to exclude any patients with potentially causative organic disorders. Patients with disorders known to cause fatigue were excluded from entry into the study. These included thyroid disorders, multiple sclerosis, symptomatic sleeping disorders, sleep apnoea, abnormal electrolytes and calcium disorders. All CFS subjects were outpatients. A full psychiatric history was also documented for each CFS subject, using the Structured Clinical Interview (SCID)(Spitzer et al, 1990). In addition to those major psychiatric disorders excluded by the Oxford Criteria, patients with all other DSM-III-R psychiatric disorders (Diagnostic and Statistical Manual for Mental Disorders- 3rd revised edition) (American Psychiatric Association, 1987), apart from simple phobias, were excluded, as well as those who reported significant symptomatic sleep disorders because of it's separate effect on fatigue. A type of fatigue does exist whereby patients complain of fatigue with accompanying hypersomnia, but who do not fulfil criteria for CFS or any psychiatric disorder (White et al, 1995). In this respect, patients presenting primarily with a sleep disorder may suffer from chronic fatigue but not Chronic Fatigue Syndrome.

One hundred and sixty seven outpatients attending a hospital chronic fatigue clinic, which has been in existence in a department of psychiatry for 11 years, were screened for the study. Ninety-six subjects did not meet criteria for the trial for the following reasons: 35 had a depressive illness, 23 had a generalised anxiety or panic disorder, 3 had significant insomnia, 16 had another psychiatric disorder, 9 had a medical exclusion, 5 were too well, 5 were too incapacitated and received inpatient treatment, 5 patients refused to participate in the trial. Those that were considered too well had recovered significantly from the CFS symptoms and no longer fulfilled the criteria. All potential subjects with CFS, and either a psychiatric disorder or sleep disturbance, were offered appropriate treatment for their co-morbid disorder. If treatment of the co-morbid disorder was successful, but they still met criteria for CFS, they were recruited into the study. Seventeen percent (11/66) had had a major depressive disorder at initial screening; 6 (9 %) initially had a generalised anxiety disorder. Ten (15 %) subjects with sleep disturbance were successfully treated by cessation of caffeine and/or a low dose of a sedative anti-depressant given at night, and entered the study. Seventy-one subjects met criteria for the trial, of whom 5 declined. Sixty six subjects gave valid, informed consent and were recruited into the study.

Table 3.1 Symptom criteria for chronic fatigue syndrome

CHRONIC FATIGUE SYNDROME (Sharpe et al, 1992) -"Oxford criteria"
* A syndrome characterised by fatigue as the principal symptom
* A syndrome of definite onset that is not life long
* The fatigue is severe, disabling and affects physical and mental functioning
* The symptom of fatigue should have been present for at least 6 months during which time it was present for more than 50% of the time
* Other symptoms may be present, particularly myalgia, mood and sleep disturbance
* Certain patients should be excluded from the definition, including: a. patients with established medical conditions known to cause chronic fatigue b. patients with a current diagnosis of schizophrenia, manic depressive illness, substance abuse, eating disorder or proven organic brain disease

Healthy Sedentary Controls

Healthy sedentary controls were recruited through posters and personal referral from staff and their colleagues at St Bartholomew's Hospital and Medical College. Prior to entry into the study, all volunteers were required to complete an activity questionnaire (Appendix C) describing in detail the number of occasions they took part in a physical activity in the previous three months; the number of times they took part in strenuous, moderate or mild activity in the average week as well as determining their attitude to activity, i.e. whether they considered themselves adequately active or sedentary. Only those considered as truly sedentary, on the scoring system, were accepted for entry into the study, i.e. they took part in no strenuous activity and exercised moderately less than once per week.

For the baseline inter-group comparison, 33 healthy sedentary controls and the 66 CFS patients, underwent the complete physiological and psychological assessment, as described below. The 66 CFS patients were those recruited for the treatment study, while the control group subjects were assessed on one occasion only. The control group and the depressed group were age, weight and gender matched with the CFS patient group.

In addition, a small group of ten outpatients with major depressive disorders were recruited by the supervising consultant or by referral from other consultants within the Department of Psychological Medicine at St Bartholomew's Hospital. As with the control group, the depressed patients went through all of the assessments during one visit. Their results on the same physiological and psychological tests were compared with those of the CFS patient group.

3.2 Psychological and symptomatic assessment

On the initial assessment a structured psychiatric interview, the Structured Clinical Interview for DSM - IIIR (SCID, American Psychiatric Association, 1987), was carried out by a qualified psychiatrist. The use of SCID requires clinical experience in and knowledge of DSM-III and DSM-III-R (Diagnostic and Statistical Manual for Mental Disorders). The

structured clinical interview (SCID) is constructed to start with questions about demographic data and the major complaint of the patient. The order of questions has been arranged to correspond to the differential diagnostic reasonings in DSM-III. The SCID provides current diagnosis of mental disorder according to the DSM-III-R as well as lifetime diagnosis and can be used reliably to differentiate major depression from generalised anxiety disorder in outpatients. All subjects then completed a total of six questionnaires to assess depression, anxiety, sleep quality, somatic symptom amplification, functional capacity general health score and mental and physical fatigue. On subsequent visits (CFS patients only) only the SCID and Clinical Global Impression change score (CGI) (Guy, 1976) were carried out by a qualified psychiatrist, blind to the treatment group, and the psychological questionnaires were completed, again by the patient, at the time of their physiological reassessment.

A combination of symptom scales and a global rating scale were used in this study. Symptom scales contain groups of items, each of which contributes partly, by describing the area covered by the scale, e.g. depression, and partly be standardising the measured dimension with which the scale operates, e.g. slight, moderate or severe depression. In contrast to this, with global rating scales, the contents and standardisation are less precise, but they are useful to include to supplement symptom scales and are they particularly useful in clinical trials (Bech et al, 1993).

All symptom scales were completed by the subjects in the same room at each assessment, in a relaxed and quiet setting (See Appendix C for scales). The purpose of all tests both physiological and psychological was clearly explained. At all stages the symptomatic questionnaires were completed prior to the physiological assessments. Every effort as made to carry out all re-assessments at the same time of day as the initial baseline assessment, to avoid potential time-related changes in mood over the period. This was also important for the physiological reassessment due to diurnal variations in physiological parameters.

The Hospital Anxiety and Depression Scale (HAD)(Zigmond & Snaith, 1983)

The HAD scale is a self-assessed mood scale, designed as an instrument to screen for clinically significant anxiety and depression in patients attending a general medical clinic. Anxiety and depression were selected as the two most common aspects of neurosis presenting in hospital practice. It avoids questions about symptoms that might be caused by physical disease (such as weight loss or sleep disturbance) and thereby overcomes inflation of psychiatric measures by physical diseases. The scale is recognised as a valid measure of the severity of these disorders of mood such that repeated administration of the scale at subsequent attendances can give useful information about changes and progress. This measure was used to assess change in mood with treatment and to assess baseline effects on treatment success.

The HAD Scale is a 14 item questionnaire with seven items composing the depression subscale and seven the anxiety subscale. There is a choice of 4 responses to each item and subjects were asked to complete it in order to reflect how they felt during the previous week. The choice of response is time based, with choices of "definitely as much" (3) to "hardly at all" (0) to questions such as, "I feel restless as if I have to be on the move" (anxiety) or "I still enjoy the things I used to enjoy " (depression). Responses are scored from 0 to 3 and separate scores up to a maximum 21 each were obtained for depression and anxiety. For both the depression and anxiety subscales, a score of 7 or less is a non - case, scores or 8 - 10 are doubtful cases and scores of 11 or more are definite cases.

Validity of the HAD was assessed by comparison with the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979) for depression and the Clinical Anxiety Scale (CAS) (Snaith et al, 1982) for anxiety. In a subsample of patients with a definite mood disorders, the correlation coefficient of the depression scale with the MADRS was 0.77 and the correlation of the anxiety scale with the CAS was 0.67. Internal consistency of the two scales was examined by calculating correlations (Spearman) between each item and the total score for the remaining items of the subscale. These correlations

ranged from 0.76 to 0.41 for anxiety ($p<0.01$) and from 0.6 to 0.3 for depression ($p<0.02$) (Zigmond & Snaith, 1993).

The Fatigue Questionnaire (Chalder et al, 1993)

Fatigue is a difficult symptom to define and many attempts have been made to measure fatigue objectively and subjectively. Fatigability, as an objective inability to sustain power, can be measured electrophysiologically, but it is not necessarily related to the subjective sensation of fatigue (May & Kline, 1988). The Fatigue Questionnaire contains a list of fourteen questions to assess physical and mental fatigue and can be used in the assessment of symptom severity, the detection of fatigue cases in epidemiological studies, and as a valid estimator of change. This scale was used to measure the severity of subjective fatigue of patients and to assess change with treatment.

Four response options are given for each item and Likert-type scoring was used to assign weights to each position with "0" being better than "3". A total fatigue score (up to a maximum of 42) is obtained by adding up all the items. The scale is subdivided into two sets of items relating to physical fatigue (questions 1 - 8) and mental fatigue (questions 9 - 14). Examples of typical questions are "do you start things without difficulty but get weak as you go on" - physical fatigue and "do you have difficulty concentrating" - mental fatigue. The Cronbach's alpha scores for internal consistency of the total fatigue scale range from 0.88 - 0.9 calculated for all items, with scores of 0.85 and 0.82 for the two sets of items for physical and mental fatigue, respectively (Chalder et al, 1993).

Relative operating characteristics (ROC) analysis was used to assess the discriminating ability of the scale across the total spectrum of morbidity, using area under the curve, giving an ROC value of 0.85 (Chalder et al, 1993). This demonstrates the ability of the scale to discern between "cases" and "non- cases". The more sensitive the scale the greater the area under the curve, where 1 = total agreement. The fatigue scale has been shown to have good face validity and reasonable discriminant validity as an estimator of change evaluated on an open treatment trial (Butler et al, 1991)

The Visual Analogue Fatigue Scale (White et al, 1995)

The status of fatigue as a physiological response, psychological perception, or a symptom of physical or psychiatric disorders remains unclear. Individuals can experience physical fatigue independent of mental fatigue, mental fatigue as distinct from physical fatigue or both together such that it becomes difficult to distinguish the exact nature of the fatigue. A visual analogue self-rating scale has been devised that allows patients to distinguish between mental and physical fatigue and also both exertional and persistent forms of these. It has previously been found that physical fatigue, particularly after exertion is more significantly severe in fatigue states than psychiatric disorders and therefore would allow us to differentiate pure fatigue disorders. The complaint of physical fatigue, especially post-exertional, may be important in differentiating post viral fatigue states from psychiatric disorders. The Visual Analogue Fatigue Scale was devised originally with CFS and depressed patients and therefore provides a useful tool for assessment and comparison with other similar groups (White et al, 1995). These measures were used to assess the different responses of the different types of fatigue to treatment. Subjects were required to score four 0 to 100mm visual analogue scales, where 0 stands for optimally healthy or non-existence of the symptom and 100 stands for a severe or strong prevalence, by placing a mark on the line at the point most applicable to how they felt in the previous week. The four lines were used to measure the principle components of fatigue - "persistent mental", "persistent physical", "exertional mental" and "exertional physical" fatigue. A score of fifty represents a normal value with high scores indicating excess fatigue.

VAS scales have been shown to have good discriminating and social validity for repeated measures (May et al, 1986). The validity of the VAS fatigue scale has been demonstrated its use with different diagnostic groups (upper respiratory tract infections and glandular fever), although very little analytical data exists as of yet. White et al (1995) found self-ratings of fatigue to be significantly higher in those with fatigue states and psychiatric disorders, than in those who were well. At 2 months after onset, subjects with fatigue states had significantly more persistent fatigue than those with psychiatric disorders (62 vs 54, $p=0.001$) and more physical fatigue (74 vs 56, $p= 0.0001$). The total physical fatigue shown to be significantly

higher in fatigue state subjects (p=0.0001) The data demonstrates that the VAS scale can discriminate between fatigue related to psychiatric disorders and a fatigue state. Persistent physical fatigue can be used to differentiate those with fatigue states from those with psychiatric disorders. The internal consistency of the VAS fatigue scale has not been assessed to date.

Two scales were used to measure fatigue since fatigue is the main symptom of this syndrome and it was important to assess it comprehensively and accurately. Some patients respond better to a Likert-type scale and others to a visual analogue scale, so using the two types allowed for greater certainty of assessing this symptom according to paients'individual preferences.

The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al, 1989)

Sleep quality is also complex and difficult to define quantitatively and objectively. Poor sleep quality can be an important symptom of many medical disorders and complaints about sleep quality are common. They are particularly associated with psychiatric disorders, and frequently accompany anxiety and stress in the general population (Karacan et al, 1983). Sleep disorders are also common in patients with chronic or unexplained fatigue (Buchwald et al, 1994; Manu et al, 1994). The PSQI was devised to provide a reliable, valid and standardised measure of subjective sleep quality and quantity, to discriminate between good and poor sleepers, and to provide a brief, clinically useful assessment of a variety of sleep disturbances that might affect sleep quality. It can also be useful to study the association between sleep disturbance and other disorders, such as age, gender, health status and medical and psychiatric variables. Subjective sleep disturbance was measured in order to examine its confounding effect on exercise treatment, and to exclude those patients with significant subjective sleep disturbance. Sleep quality includes quantitative aspects of sleep, such as sleep duration, sleep latency or number of arousals, as well as more purely subjective aspects, such as "depth" or "restfulness" of sleep.

The PSQI assesses sleep quality during the previous month. The scale consists of 19 self-rated questions to assess a wide variety of factors relating to sleep quality, including estimates of sleep duration and latency, and the frequency and severity of specific sleep-related problems. This includes questions such as, "during the past month, have you had trouble sleeping because you - (a) cannot get to sleep within 30 minutes or (b) wake up in the middle of the night or early morning". Response choice range from "not during the past month" to "three or more times per week", with grades in between. These 19 items are grouped into 7 component scores sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication, daytime dysfunction - each weighted equally on a scale of 0 to 3. Sleep efficiency and number of hours sleep per night are also rated from a 0 - 3 point scale. The seven components are added together to yield a global PSQI score ranging from 0 - 21, with higher scores indicating poorer sleep quality.

The seven component scores had an overall reliability coefficient (Cronbach's alpha) of 0.83, indicating a high degree of internal consistency. This implies that each of the 7 components appears to measure a particular aspect of the same overall construct, i.e. sleep quality. Test-retest reliability gave no significant differences on paired t-tests, with the questionnaire completed on 2 occasions, 28 days apart with no intervention in between. Validity was determined by comparing PSQI estimates of sleep variables with those obtained by polysomnography. T-tests showed no difference between PSQI estimates and laboratory findings for sleep latency ($r = 0.33$, $p < 0.001$). A global PSQI score > 5 provided a sensitive and specific measure of poor sleep quality, relative to clinical and laboratory measures as well as by comparison of healthy subjects with those with known sleep disorders. (Buysse et al, 1989)

Barsky Amplification Scale (Barsky et al, 1988)

Somatosensory amplification refers to the tendency to experience somatic sensations as intense, noxious or disturbing. It can involve either a heightened attentional focus on bodily sensations or a tendency to select out and concentrate on some relatively mild and infrequent sensations. Amplification encompasses a wide range of somatic stimuli and bodily states, and

is not necessarily limited to those sensations symptomatic of disease. In this respect some individuals can also be more inclined to recognise and report both psychological and somatic symptoms, such that they amplify all forms of distress, verifying the close relationship between psychological symptoms of emotional distress and somatic symptoms of bodily distress. Somatosensory amplification can be measured with this self-report questionnaire to assess the tendency of an individual to amplify a broad range of bodily sensations, which has been shown to have associations with anxiety, depression and hostility and to be a predictor of impairment of functioning (Barsky et al, 1988). This scale was used to assess whether "somatization" alters treatment efficacy or changes with treatment. The amplification scale consists of five self-report questions. Patients or subjects were asked to rate how characteristic each of the items was of them on a five point scale from 0, ("not at all") to 4, ("extremely"), giving a maximum score of 20. The questions relate to sensations of pain, noise, hunger and cold/heat. Intra-scale reliability (internal consistency) was 0.72, according to the Cronbach's alpha method. The test-retest reliability was assessed by re-admistration of the scale to 52 patients over periods from 1.5 to 5 weeks and this gave a coefficient of reproducibility of 0.85. Evidence of its predictive validity was obtained from a high correlation ($r = 0.58$, $p=0.0001$) with DSM-II hypochondriasis scale (Barsky et al, 1988)..

Short Form 36 (SF36) Health Survey Questionnaire

Traditional measures of morbidity to assess the effects of different health care interventions that can influence a wide range of variables, such as physical mobility, emotional well-being, social life, and overall well-being, are generally agreed to be to restricted (Brazier et al, 1992). General health measures can be used to examine the relative burdens of different diseases and the relative benefits of different treatments, in a different way than disease specific or treatment-specific measures. The SF 36 is a short form of the Medical Outcomes Survey (MOS) questionnaire, and is a standardised, comprehensive and brief, self-rated measure of how people perceive their health and capacity (Ware & Sherbourne, 1992). The Health Survey Questionnaire represents the health concepts most frequently included in health surveys - physical, social and role functioning, mental health, and general health perceptions - as well as two additional concepts - bodily pain and vitality. Each of the eight health

concepts were scored separately, from 0 to 100, with low scores indicating poorer health and capacity.

Physical function was assessed with 10 items, ranging from less demanding functions like bathing and dressing, up to the most vigorous activities of running, lifting heavy objects and strenuous sports, with walking, climbing, bending and moderate sport falling in between. Low scores indicated a lot of limitation in all physical activities, and high scores indicated that all types of physical activities could be performed without limitations due to health. Three choices of response were given for each activity, from "limited a lot" to "not limited at all". The first of two function scales physical role, was constructed from questions about health-related limitations in the type or amount of work. Low scores indicated problems with work or other daily activities as a result of physical health and high scores indicated no such problems in the previous 4 weeks. This included 4 questions, such as "due to health, have you accomplished less than you would like to" with yes/no responses for each. Bodily pain assessed the frequency of bodily pain or discomfort and the extent of interference with normal activities because of pain using 2 questions. The answers ranged from "not at all" to "extremely" A low score indicated very severe and extremely limiting pain, and a high score implied no pain or limitations due to pain in the previous 4 weeks. General health perception used 4 questions using 5 response choices ranging from definitely true to definitely false on questions such as, "I am as healthy as anybody I know". Low scores indicate a belief in poor personal health that is likely to get worse and high scores, a belief in excellent general health. A four-item measure of vitality was used to assess subjective well-being, using 5 response choices from "all of the time" to "none of the time". The scores ranged from feeling tired and worn-out all the time (low) to feeling full of pep and energy all of the time (high) in the previous 4 weeks. A typical question would be "Do you feel worn out" or "Do you have a lot of energy". The social function item assessed health related effects on social activity using a 5 choice scale ranging from "not at all" to "extremely". The questions enquired as to what extent or how much of the time physical or emotional health interfered with social activities, such as visiting friends. High scores indicate that physical and emotional problems have not interfered with normal social activities in the past 4 weeks. The

second function scale assessed role limitations because of emotional problems (role emotional) with 3 questions and a yes/no response choice to questions asking to what extent emotional health has caused them to, "accomplish less than you would like". Low scores indicate problems with work or other daily activities as a result of emotional problems while high scores indicate no problems in these areas. The mental health scale includes one or more items from each of the four major health dimensions (anxiety, depression, loss of behavioural or emotional control and psychological well-being). Typical questions would be "Have you felt down-hearted and blue" or "Have you been a happy person". The response choices ranged from "all of the time" to "none of the time". Low scores indicated feelings of nervousness and depression all of the time and high scores indicated feeling peaceful, happy and calm in the past 4 weeks.

The item total correlation coefficients for the 36 items within the 8 health scales ranged from 0.55 to 0.78 and Cronbach's Alpha exceeded 0.8 on all eight scales, ranging from 0.80 to 0.92. both providing evidence of internal consistency. Clinical validity (construct) was shown by clear differences in self reported health between the general population and patients with four common conditions and by a high level of agreement between SF36 scores and general practitioners' perceptions of symptom severity (Garratt et al, 1993).

Clinical Global Change Scale (Guy, 1976)

The main outcome measure in the treatment study was the Clinical Global Impression change scale (CGI). Global rating scales are extremely simple instruments, which require little time for assessment and recording, but they do not provide the same details as symptom rating scales. Therefore it is generally recommended that global rating is used in conjunction with symptom rating scales (Bech at al, 1993). The CGI is a frequently used and validated self-rated measure of severity of illness or overall change since admission into a study or compared to treatment onset. Global scales of change are bipolar scales, in that they use, for example, the following categories: 3 = marked improvement, 2 = moderate improvement, 1 = slight improvement, 0 = no certain improvement, -1 = slight deterioration, -2 = moderate deterioration, -3 = marked deterioration. For ease of use

and for scoring purposes, the numerical values tend to shift so that the scale ranges from 1 = marked improvement/very much better to 7 = marked deterioration/ very much worse. The use of scales for change requires a good retrospective and global memory and is therefore most appropriate for short-term therapeutic studies, such as this one (Guy, 1976). The span for global improvement is "since admission into the study" and not from the last rating period. This nature of global scales makes them relevant and meaningful in evaluation of therapeutic effect. Due to the lack of definition of the scales and standardisation studies, they have played only a modest role in many scientific investigations within clinical psychiatry. The validity can be verified by its use in several trials (Ahlfors et al, 1980; Heikkila at al, 1981). Provided that the assessor is a trained clinician who is familiar with the medical aspect of the illness, the scale by definition becomes valid, since global assessment of a disease condition is part of traditional psychiatry. Under these conditions, the reliability becomes very good, generally better than symptom rating scales (Bech et al, 1993).

3.3 Physiological Assessment

Visit One

All physiological assessments were carried out at the exercise physiology laboratory at the National Sports Medicine Institute. Full explanations given of the test procedures and trial requirements were again given prior to the assessment. Lifestyle details were taken by the senior physiologist including questions on smoking and drinking habits, duration and initial onset of illness, premorbid and current activity levels and any activity that they found particularly difficult. Patients were asked to refrain from eating for at least one and a half hours prior to their appointment for comfort to eliminate any potential adverse effects of the exercise or anxiety about the tests on digestion, and they were instructed to bring comfortable walking shoes and loose clothing.

Body composition

The percentage of body fat was measured using a Harpenden skinfold calliper. Three skinfold measurements were taken at each of four sites - triceps, biceps, subscapular and suprailiac - according to the method by Durnin and Wormersley (1974). The average of each of the four site measurements was added to give a total four site skinfold score in millimetres. This measurement was used to assess baseline body fat levels in relation to general population norms and to monitor any changes in body fat levels during the course of the treatment

Resting lung function

Forced Vital Capacity (FVC) and Forced Expired Volume in 1 second (FEV1) were measured using a Vitalograph Spirometer (Buckingham, England). Holding the tubing and mouthpiece patients were instructed to take a deep breath and then to exhale completely and forcefully into the machine until they felt their lungs were completely empty. They were required to repeat this test three times in their own time and the best score was taken. This gave a measure of FVC (litres/minute), FEV1 (litres/minute) and the ratio of FEV1 to FVC.

This was to assess basic lung mechanics in terms of ability to expire forcefully and to discern that there were no underlying airway obstructions that might hinder exercise performance.

Isometric quadriceps strength

Voluntary and stimulated isometric maximal voluntary contraction (MVC) was measured in the quadriceps femoris muscle of the dominant leg. Patients were seated in a specially adapted rigid, straight back chair. The back was adjustable to alter the seat length such the lower limb below the knee was allowed to hang freely at 90 degrees. Patients were held in position by a large strap around the pelvis. An inextensible strap was attached around the ankle (just proximal to the malleoli) which was attached to a strain gauge and amplifier at the back of the chair. The distance from the strap to the strain gauge was again adjusted to maintain the 90 degree knee flexion. Two large pad electrodes (8 cm x 12 cm) were strapped over the proximal and distal portions of the anterior aspect of the thigh for percutaneous twitch stimulation. The two pad electrodes were attached to a Digitimer electrical stimulator driven by a Digitimer Trigger Generator such that 200-350 volt impulses and 50 usec duration were initiated at 1HZ frequency. Trial stimulations were applied at rest with the subjects asked to rate on a scale of 1 to 10 whether they found it painful or uncomfortable. Maximum voluntary contraction (MVC) was measured when the patients were asked to push against the ankle strap with as much force as possible holding for approximately 3 seconds. Verbal encouragement was given for each trial and 15 seconds rest was allowed between contractions. They performed five repetitions, with twitch stimulations added on trials 2 and 4.

During a truly maximum contraction no extra force is generated by the stimulation in addition to the voluntary force. This technique was used to ensure maximal activation of the quadriceps muscle by over-riding any central inhibition and has been used previously with patient groups (Rutherford et al, 1986; Gibson et al, 1993). In the original protocol for this technique, where extra force is generated by stimulation, the true maximum can be estimated from the height of the extra force recorded, relative to the height of the twitch before the

voluntary contraction. The development of any additional twitch force on the stimulated trials reflected a submaximal contraction.

However, the equipment available for the current study could not allow for accurate measurement of the height of the extra force generated by the stimulation relative to the height of the twitch unstimulated (i.e. voluntary maximal contraction). Results for the MVC were measured in Newtons (N) as well as recording whether the highest MVC was achieved with or without twitch interpolation. This is an adaptation of the twitch interpolation technique described by Edwards et al, (1977) whereby it is only possible to determine the subject's ability to maximally contract their quadriceps voluntarily, i.e. without stimulation. In this respect the stimulation was used to determine if there was a central inhibition, and by adding extra stimulation to over-ride this, a closer representation of the muscles maximal capacity could be gained. This peak force was recorded as well as whether this was achieved with or without stimulation, so that we could then record the number of subjects who could reach their highest value voluntarily, or with the addition of electrical stimulation, to more fully activate the muscle.

Treadmill familiarisation

To relieve any anxiety about the test and treadmill exercise, all CFS patients were thoroughly familiarised with the test procedure on visit one, prior to performance of the walking test on visit 2. The control and depressed groups did all of the tests in one visit. They were introduced to walking on a Powerjog M30 Medical Treadmill (Sport Engineering Ltd) at increasing speed up to the test speed of 5 kilometres per hour ($km.h^{-1}$), with a mouthpiece in place. Instruction was also given on how to step off the treadmill when the subject needed to stop and on the use of the Rating of Perceived Exertion (RPE) scale (Borg 1970). The procedures for the fingertip blood sampling for lactate analysis were also explained as well as the incremental progression of the test and the requirements from them.

Visit Two

Visit two was approximately one week after visit one and subjects were again requested to refrain from eating for one and a half hours before their appointment. Height was recorded (in metres) with a Seca stadiometer and weight (in kg) using a calibrated Seca scales. These were used to calculate the Body Mass Index (BMI) from the formula weight (kg) divided by height $(m)^2$. Thumbprick capillary blood samples (approximately 20 microlitres) were taken with the patients seated for determination of resting blood lactate concentration (in mmol/litre) using a GM7 automated blood analyser (Analox Medical Instruments). The analysis is based on the conversion of lactate and O_2 to pyruvate and H_2O_2 catalysed by lactate:oxygen oxidoreductase. The maximum rate of oxygen consumption is directly related to the lactate concentration in the sample. Samples were analysed in duplicate

Three electrodes were placed on the chest, one on each side at the base of the sternum and one in the clavicular area. Heart rate was recorded throughout the test using a 3-lead ECG (Hewlett Packard 40120A) which gave a continuous display of heart rate and V5 wave. The ECG recording was also interfaced with the on-line gas analyser and was displayed on the print-out throughout the test. Expired air was analysed continuously using an on line Jaeger EOS Sprint gas analysis system (Erich Jaeger UK Ltd). Patients breathed through a low resistance lightweight valve (Jakemen & Davies, 1979) attached via lightweight tubing to the EOS sprint system. Minute ventilation was measured by a pneumotachograph. The percentage of oxygen (O_2) and carbon dioxide (CO_2) in the expired air were sampled from the collection bag and analysed every 30 seconds by a Zirconium O_2 analyser and a paramagnetic Infrared CO_2 analyser, respectively. This enabled continuous monitoring of oxygen consumption and carbon dioxide production in litres per minute and millilitres per kg per minute. Test procedures and requirements were again explained to the patients.

The treadmill speed was gradually increased to the test speed of $5km.h^{-1}$ and the test began when the subject appeared comfortable, which took about 1-2 minutes. Slope was increased every 2 minutes from zero to 5% initially, and then in 2.5% increments. Subjects were asked

to rate their perceived exertion using an unmodified Borg scale (Borg, 1970) in the last 30 seconds of each 2 minute stage. When they indicated an RPE of 14 (between "somewhat hard" and "hard"), on the scale, a fingerprick capillary blood sample was taken for blood lactate analysis. Patients were encouraged to continue to volitional exhaustion or symptom limited maximum. The test was terminated as soon as they stepped off the treadmill and recovery heart rate was recorded for 5 minutes. Peak VO_2 and heart rate were recorded as well as percentage of age predicted maximum heart rate reached, calculated from the formula 210 - (age x 0.65) (Jones, 1988). Aerobic capacity was measured in absolute ($l.min^{-1}$) and relative ($ml.kg^{-1}.min^{-1}$) terms. A final blood sample was taken 3 minutes after the test for determination of peak blood lactate concentration.

Before leaving the laboratory the CFS patients were given an activity diary to record their habitual activity pattern during a normal week. They were also given instructions on how to record their pulse rate and asked to record their resting pulse rate over the week.

Calibration

The EOS Sprint system was calibrated 30 minutes prior to each test and again no more than 10 minutes prior to the test. Calibration of the analysers was done in two stages by passing a sample of a known certified gas mixture through, at a controlled flow rate of 1 litre per minute. The first "zero point" gas, containing 100% nitrogen and no oxygen or carbon dioxide, was used to set the baseline by checking that the analyser recorded a zero gas concentration for this mixture. As soon as the zero point was stable, the O_2/CO_2 mixture was automatically let through. The second calibration gas contained a mixture of approximately 5% CO_2 and 15% O_2. This mixture was used to set a second reference point at values close to those expected during physiological assessment. The computer would then use the two-point calibration to calculate an actual regression line. The pneumotachograph was calibrated by passing a 2 litre volume of ambient air through ten times (20 litres) using a 2L syringe. Using the expected and actual value a correction factor was automatically calculated by the computer.

The treadmill was calibrated once a month. This was done by first measuring the belt length using 4 separate measurements. A mark was placed on the belt so that the number of revolutions of the belt could be counted as it passed a set point on the side. The treadmill was then run at set speeds from 4 to 20 $km.h^{-1}$ and the calculated belt speed derived from the formula:

$$\text{Belt speed} = \text{Belt length(m)}/1000) \times \text{No. revolutions(n)}/\frac{\text{time for no. laps(s)}}{3600}$$

$$\text{Belt speed} = \frac{14.616n}{t}$$

where 4.06 m = belt length

n = no. of laps timed

t = time for n laps in seconds

The polar heart rate monitors that were given to subjects for recording of home exercise sessions were calibrated prior to use. This was done manually while also showing them how to record pulse at the wrist or carotid artery in the neck. With the subjects seated and relaxed and with a stable pulse, beats were counted for 15 seconds and multiplied by 4 to give heart rate in beats per minute, which was compared with the value recorded on the polar monitor. Values were also compared with the pulse count automatically measured by the 3 – lead ECG.

Randomisation - CFS patients only

Prior to the study sixty-six pieces of paper were coded with either an E (Exercise Group) or an F (Flexibility Group), 33 in each group. The papers were then placed in envelopes coded 1 to 66, the order of envelopes being determined by random number tables. Once a patient completed the initial screening and assessment, the next envelope was opened by an independent staff member, not connected to the study. This allowed for random allocation of all 66 CFS patients into the two treatment groups.

The psychiatrist who conducted the psychiatric retesting was not informed about the treatment group of the patient. Patients were informed that both groups involved a form of treatment, which was explained to them, and that the researchers were not aware whether one was better than the other.

2.4 Treatment

Exercise group

Exercise treatment followed the basic principles of exercise prescription (ACSM, 1990) adapted to the subjects current capacity. Patients attended the Exercise Physiology Laboratory on a weekly basis for twelve weeks for exercise, flexibility and relaxation sessions and to receive the following weeks exercise prescription. All weekly sessions were supervised by a qualified exercise physiologist. Exercise intensity and duration was individually tailored but most patients began at an intensity of 40% of their maximum aerobic capacity which equated to approximately 50% of their individual heart rate maximum reached in the walking test. Progression was determined by individual ability.

The initial aim was to establish a regular pattern of exercise, without over emphasis on the duration to start with, such that patients were encouraged to exercise daily, at least five days per week. Patients were encouraged to make their exercise session a part of their daily routine, setting aside the time and planning in advance, particularly with regard to the best time of day to exercise. Sessions initially lasted 5 to 15 minutes and were progressed by increasing the duration by 1 - 2 minutes per week up to 30 minutes and then by increasing the intensity to 50% and then 60% of their maximum aerobic capacity. Target heart rates for the exercise sessions were calculated for each individual and they were given portable heart rate monitors (Polar Favour Sports Testers) to monitor and record the intensity during their prescribed exercise sessions, and to ensure that they reached, but did not exceed, their target heart rate. They were also taught how to measure their heart rate manually to give them a better understanding and for longer term application.

Other exercise devices were also introduced during the programme and patients were also encouraged to use other modes of exercise at home, such as stationary and outdoor cycling and swimming. On the laboratory visits patients exercised on the treadmill and the cycle, and occasionally the rower or stepper, within their target range for up to 30 minutes. They were also given instructions sheets to include some simple stretching exercise at the beginning and end of their exercise session. They were taught the basics of passive stretching and given a selection of exercises for each of the main muscle groups to be stretched. This included exercise for the upper and lower leg, the arms and shoulders, the chest and upper back and the neck.

Subjects were advised not to exceed prescribed activity levels during a good phase of the illness. If they reported fatigue in response to a new level of exercise, they were advised to remain at the same level for an extra week and to increase the exercise when the symptoms regressed. Stretching and relaxation was included in this group in order to establish correct exercise habits and to allow comparison of similar treatments on all aspects except the aerobic exercise.

Flexibility Group

Patients in this group also attended the laboratory on a weekly basis for twelve weeks for flexibility and relaxation sessions. Each subject was taken individually through a stretching routine by the exercise physiologist and given an instruction sheet with diagrams of exercises that they should perform at home. As described above this involved a selection of passive stretching exercises for all the major muscle groups, with alternative and with a wider range of exercises added through the programme. The general instructions involved holding each position for a minimum of 15 seconds and repeating each exercise twice. Exercises were included for the upper and lower leg, the arms and shoulders, the chest and upper back and the neck. Relaxation sessions were carried out in a quiet, darkened room led by the exercise physiologist and involved controlled breathing, progressive muscular contraction and relaxation followed by mental visualisation aided by appropriate music.

Patients were encouraged to set aside 10 minutes each day for stretching or relaxation. The time was increased up to 30 minutes per day, 5 days per week, as more exercises were added. They were told to avoid any aerobic activities that were not already being undertaken. This was explained as any strenuous activity that caused them to get out of breath, that noticeably increased their heart rate for more than a few minutes, or caused them to sweat/perspire, i.e. brisk walking, jogging, swimming, cycling.

Activity Diaries

All patients kept a weekly activity diary (Appendix D), recording details of the type and duration of exercise, time of day and how they felt during and afterwards. This was discussed with each individual at the beginning of each weekly visit before deciding on the each week's treatment.

3.5 Reassessment and follow-up

Reassessment after treatment

After twelve weeks, all patients attended the laboratory for physiological and symptomatic reassessment, as performed previously except that all tests were carried out in one session. Prior to the physiological testing, each patient completed the six self-rated questionnaires. Resting lung function, total skinfold measurement, isometric quadriceps strength, and treadmill walking were carried out as in the initial assessment. Capillary blood samples were taken again when they indicated an RPE of 14 and also at the same stage as the original blood sample if the RPE ratings had altered. During the same week patients also attended the psychiatrist for a SCID interview and to complete a CGI change score.

Crossover from Flexibility to Exercise

Following their reassessment, patients in the flexibility group were given the option of continuing into the exercise treatment group. Exercise sessions were carried out exactly as for the group doing the exercise treatment first, involving a weekly progression of duration and intensity of exercise, with activity diaries maintained throughout. After twelve weeks on this treatment, patients were reassessed physiologically and symptomatically, as described

above. In this respect, the patients who crossed over to the exercise treatment after the flexibility programme did not have a 3 month follow-up after flexibility alone. This allowed us to assess whether a combination of treatments, or a gradual introduction to aerobic or more strenuous exercise, via stretching, was more effective. It also allowed a further assessment of the exercise treatment to ascertain whether a second group on the same treatment but with a different initial phase would have the same response, but ideally an assessment at three months after completion of the flexibility programme would be desired.

Three Months Follow-up

After the post-treatment assessment (at 12 weeks), all patients were given instructions on how to continue and progress with exercise. Some instructions on simple upper body muscle conditioning and modified circuit exercises were included at this stage. Patients were also permitted to contact the exercise physiologists or to join in an occasional exercise sessions with another patient on the programme should they feel the need to. Three months after the end of treatment reassessment, all patients returned for a full physiological and symptomatic reassessment as before. This was in order to determine if any improvements achieved during either or both treatments were being maintained.

One Year Follow-up

Approximately one year after the three month reassessment (i.e. 18 or 21 months after baseline assessment for the exercise and flexibility groups, respectively, a letter was sent to all patients. This enquired whether they were still exercising, whether they had returned to work or study and/or premorbid activity levels. They were also asked to complete a visual analogue fatigue scale and a Clinical Global Impression Scale.

3.6 Outcome measures

The CGI change scale is a self-rated measure of overall change, compared to study onset, with seven possible scores from "very much worse" (7) to "very much better" (1). Subsidiary

outcome measures included assessments of strength and fitness, symptoms and functional capacity, as described above.

Analysis

The first stage of analysis involved exploration of the distribution of the data using a one-sample Kolmgorov-Smirnov test. This goodness of fit test allows for testing the degree of agreement between the distribution of an observed set of values with a specified theoretical distribution. The resulting K-S value enables the determination of the use of parametric or non-parametric tests for comparison of the means. Given the sample sizes involved in the current study, a K-S value above 0.2 implied that parametric tests should be used for the comparison, and non-parametric test should be used on any distributions with a K-S value below this. If the data had a normal distribution, t-tests were used for comparison of the means of unmatched samples, applicable to both interval or ratio data. The aim of these tests was to compare the amount of variability due to predicted differences in scores between the two groups as against the total variability of subjects' scores. In any cases where the data was not normally distributed, the non-parametric equivalent of the t test, the Mann-Whitney test was used. This test puts the 2 groups of scores together and rank orders all of them, and then checks whether one group has mostly low scores, while the other has mostly high scores. Therefore baseline and post-treatment comparisons between groups used either t tests or Mann-Whitney tests, depending on the distribution. If the data was normally distributed then mean and standard deviation is shown in the tables, whereas, if not normally distributed, the median and interquartile range are shown. For comparison of the same group before and after treatment, i.e. matched pairs analysis, the Student's t test (parametric) and the Wilcoxon test (non-parametric) were used depending on the distribution. In all cases a P value of 0.05 or less was considered to be significant, so as to reject the null hypothesis. However, higher P values are shown in some cases to display a "trend" towards significance.

The CGI change score was analysed categorically, with a score of 1 or 2 ("very much" or "much" better) considered a clinically important improvement, versus CGI scores of 3 - 7 ("a

little better" or worse than that). We compared the proportions, rating themselves as better after three months of each treatment, in those who completed treatment as well as by the intention to treat, using a Chi-Square (with continuity correction) test for two independent samples. This test allows a comparison of the proportion of scores from each group falling into the various categories. We also compared all outcome variables within each group, before and after treatment. The effects of the two treatments on the sub-maximal responses to the treadmill test were compared by examining the mean heart rate and RPE against sub-maximal treadmill test stages in the middle third of the walking test between 6 and 12 minutes, both at baseline and at the end of treatment. At three months follow up, the proportion making a significant improvement, as well as and other outcome measures, were compared to the onset of treatment. The cross-over group, who received flexibility and relaxation training, followed by exercise therapy, provided an immediate re-test of the efficacy of this treatment. They were followed up in the same way as the original exercise group with the same outcome measures. At one year follow-up, we reported the proportion feeling better after completing exercise treatment.

CHAPTER FOUR : RESULTS

4.1 Comparison between patient and subject groups at baseline

4.1.1 Healthy sedentary controls and CFS patients

A total of 30 healthy sedentary controls were recruited into the study for comparison on physiological and symptomatic measures with the CFS patient group.

At presentation to the department, all potential CFS subjects with psychiatric disorder or sleep disturbance were offered appropriate treatment. If the treatment was successful, but they still met criteria for CFS, these patients were recruited into the study. Seventeen percent (11/66) initially had a major depressive disorder and 9% (6/66) initially had a generalised anxiety disorder. All 17 were successfully treated for these psychiatric disorders before entering the study. Fifteen percent (10) subjects with sleep disturbance were successfully treated by cessation of caffeine and low-dose sedative anti-depressants at night, and then entered the study. The 66 patients screened and recruited for the baseline comparison formed the two groups for the treatment study.

The main characteristics of the CFS and control groups are given in Table 4.1. Groups were matched for age, weight and gender, and there were no significant differences between groups in any other characteristics, except for height, whereby the CFS patients were significantly taller ($p=0.04$). Despite being very inactive, all subjects fell within the optimum range for BMI of 20 - 25 kg/m_2 with both groups having a very similar total skinfold measurement. Thirty-two (48%) of the 66 CFS patients were taking medication at the time of assessment, with 20 taking full-dose antidepressants, 10 taking antidepressants at hypnotic doses, and 2 were on other medication.

In all of the results tables, if the data was normally distributed then mean and standard deviation is shown in the tables, whereas if not normally distributed, the median and interquartile range are shown.

Table 4.1. Characteristics of healthy sedentary controls and CFS patient groups. Values are mean and standard deviation (SD) if normally distributed (K-S > 0.2), or median + interquartile range (IQR), if not normally distributed (K-S < 0.2).

*** signifies a significant difference ($p < 0.05$), comparisons are otherwise non-significant**

Characteristic	CFS Patients (n=66)	Sedentary Controls (n=30)
Age (years)	37.2 (10.7)	36.8 (11.1)
Height (cms)	169.5 (162.9-176.1)	163.3 (158.7-167.9)*
Weight (kgs)	65.0 (53.9-76.1)	64.7 (54.8-74.6)
Body Mass Index (kg/m^2)	22.9 (20.2-25.7)	23.4 (29.8-26.0)
Total skinfold (mm)	52.6 (36.8-68.5)	50.6 (38.4-62.8)
Female/male	49/17	22/8

Physiological comparison

Results of the physiological assessments for the CFS patients and healthy controls are shown in Table 4.2. There were significant differences between the groups in all measures, except in resting lung function measures, with the CFS patients having a lower aerobic capacity, indicated by the lower relative and absolute VO_2 peak and maximum ventilation. In the CFS group, the mean VO_2 peak was 28.2 (6.9) and 37.5 (8.1) $mls.kg^{-1}.min^{-1}$ for females and males, respectively and in the control group mean values were 31.7 (5.8) and 40.5 (5.3) $mls.kg^{-1}.min^{-1}$. The CFS group terminated the test at a significantly lower maximum heart rate, representing 91.6% of their age predicted maximum heart rate compared to 97.6% in the control group. This reduced exercise capacity was also indicated by the significantly

lower peak blood lactate and test duration, whereby the control group continued exercise for almost 3 extra minutes (2 further gradients). Maximum isometric leg strength was also significantly reduced in the CFS patients (461 vs 336 Newtons). These were taking the highest values recorded in both groups, with 65% of the CFS group and 80% of the control group reaching this without stimulation, i.e. their own voluntary maximum level. There were no differences between groups on any measures of resting lung function. Recovery heart rate taken 3 minutes after the treadmill test was higher in the control group than in the CFS group (117 vs 110 BPM).

Table 4.2 Physiological variables of healthy sedentary controls and CFS patient groups

Values are mean (SD) or median (IQR); p > 0.05 is not significant (ns).

Variables	CFS patients (n=66)	Sedentary controls (n=30)	Significance
VO_2 peak ($ml.kg^{-1}.min^{-1}$)	30.6 (8.3)	34.1 (6.8)	0.05
VO_2 peak ($l.min^{-1}$)	1.9 (1.6-2.2)	2.1 (1.7-2.5)	0.04
Ventilation max ($l.min^{-1}$)	69.8 (56.7-82.9)	82.4 (66.4-98.5)	0.05
Heart rate max (BPM)	171 (18)	181 (14)	0.004
% predicted max HR	91 (8.8)	97 (5.2)	<0.001
Recovery heart rate (BPM)	110 (17)	117 (17)	0.05
Test duration(minutes)	10.0 (3.6)	12.8 (3.1)	<0.001
Total RPE	69 (21)	80 (19)	0.01
Blood lactate at RPE 14 ($mmol.l^{-1}$)	2.8 (1.6-4.0)	3.5 (2.2-4.8)	0.001
Peak blood lactate ($mmol.l^{-1}$)	5.4 (2.2)	6.7 (2.1)	0.005
FVC ($l.min^{-1}$)	3.9 (0.8)	3.9 (1.1)	ns
FEV1 ($l.min^{-1}$)	3.1 (0.7)	3.1 (0.8)	ns
FEV1/FVC ratio	79.8 (8.0)	80.2 (8.2)	ns
MVC (Newtons)	336 (118)	461 (114)	<0.001

Oxygen uptake and perceived exertion rating at submaximal stages of the treadmill test are shown in Figures 4.1 and 4.2, respectively. As can be seen, perceived exertion scores were significantly higher ($p < 0.02$) on all submaximal stages of the test between 2 and 12 minutes,

in the CFS patients compared to the control group with the control group indicating a lower perceived rating of exertion at all levels. Comparisons at 16 and 18 minutes on any of these measures were not done as the represented maximal, rather than submaximal levels of exertion for those who continued the test to for this duration and the numbers in either group continuing the test to these stages were small. Differences in submaximal oxygen uptake were significant only at 6 ($p=0.05$), 8 ($p=0.04$) and 14 (0.02) minutes. Submaximal heart rate did not differ between the two groups on any stage of the test.

Symptomatic comparison

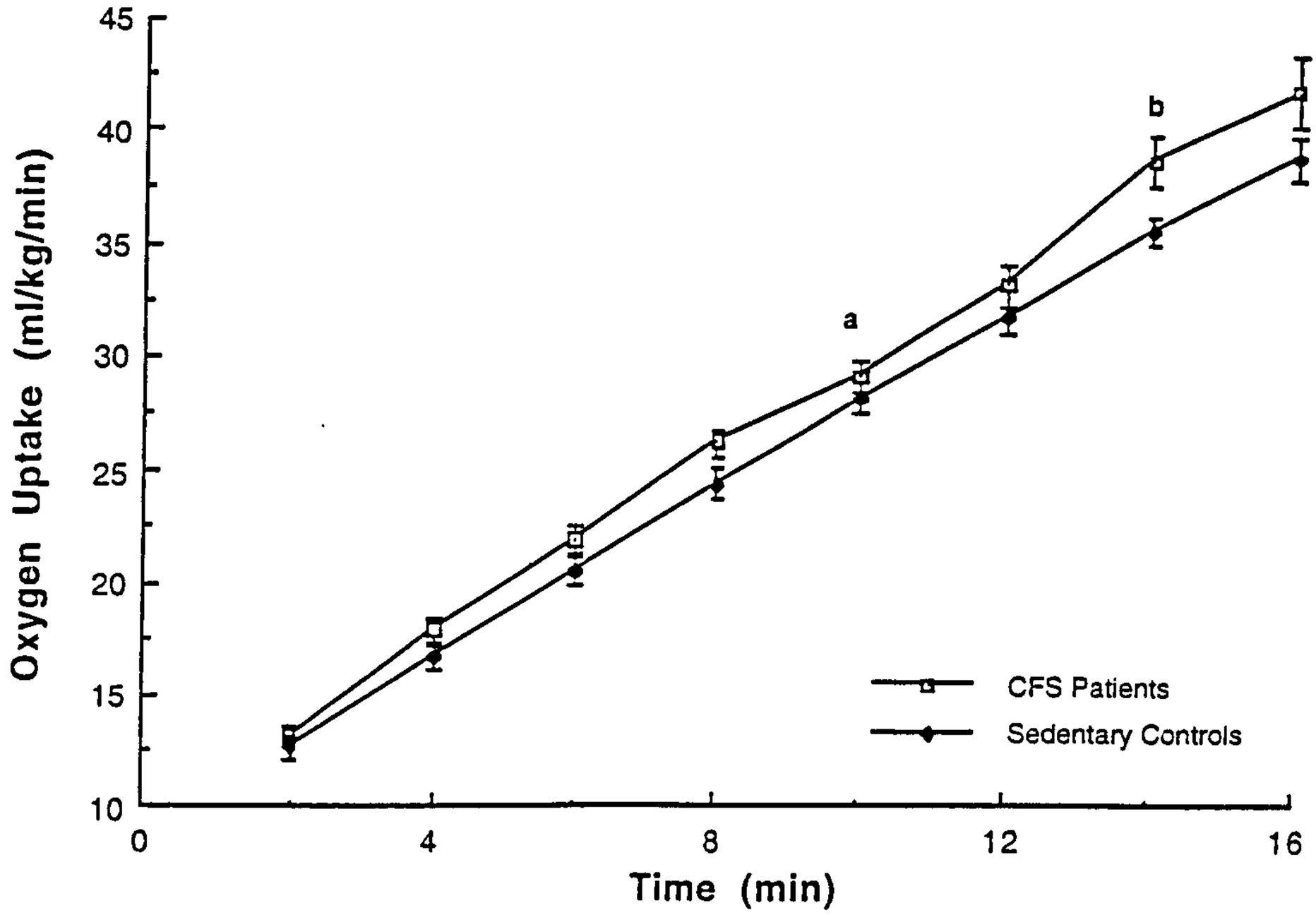
Table 4.3 shows the results of the symptomatic measures of the two groups. There were highly significant differences between groups on all measures of fatigue, both visual analogue total, physical and mental fatigue and the Chalder fatigue scales. In addition the CFS patients scored significantly lower on measures of general health and well-being, as indicated by a lower SF36 total score and lower scores on physical function and role, bodily pain, vitality, social function, mental health. The implications of these will be discussed later. The CFS group also showed a significantly higher level somatosensory amplification (Barsky score). However, there were no differences between the patient and control groups in emotional role as measured by the SF36, HAD depression and anxiety, or PSQI sleep quality total score.

Table 4.3. Symptomatic variables in healthy sedentary controls and CFS patient groups

Values are mean (SD) or median (IQR); p>0.05 is not significant

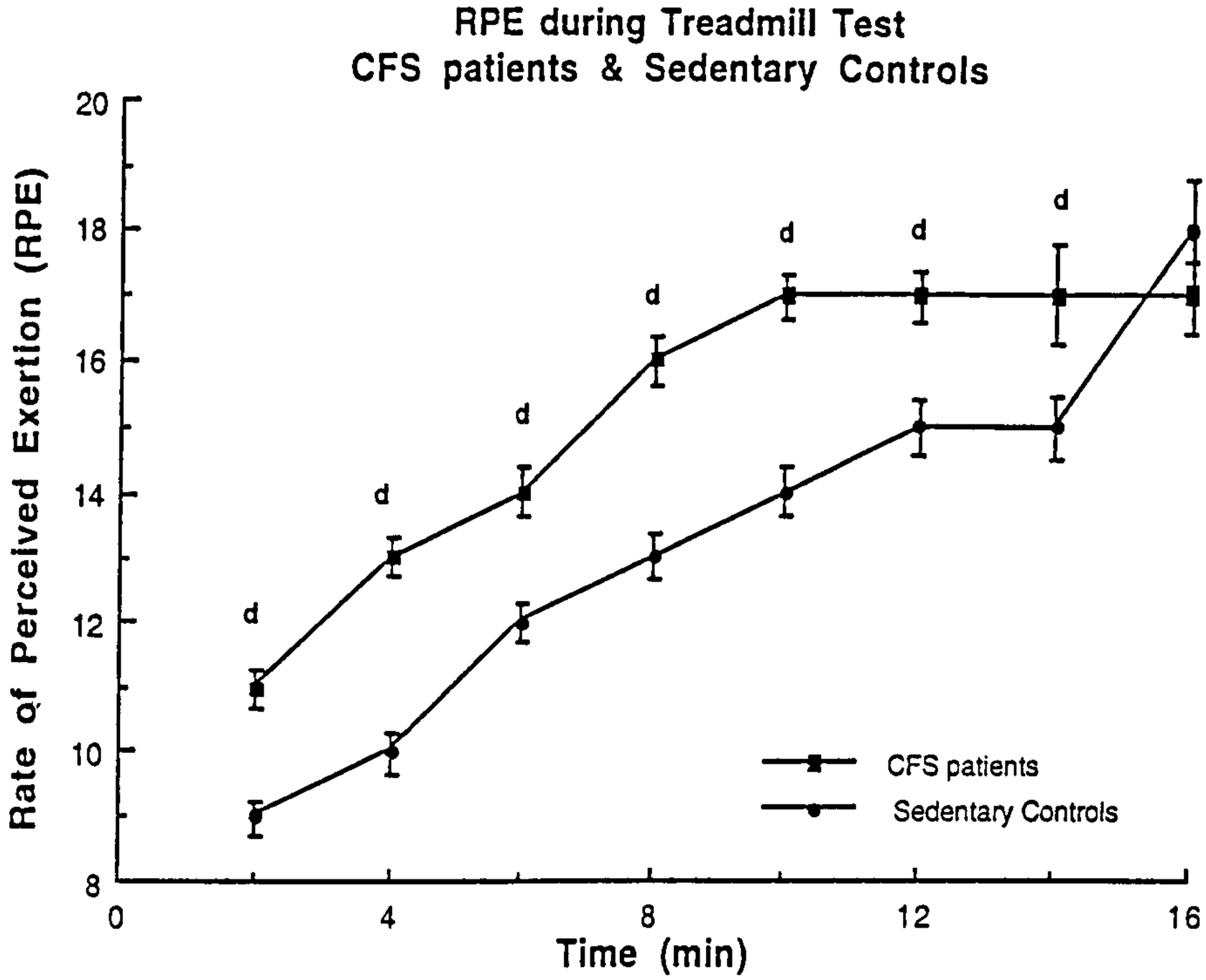
Variable	CFS patients (n=66)	Sedentary controls (n=30)	Significance
V/A total fatigue	318 (47.4)	214 (58.1)	<0.001
V/A physical fatigue	168.5 (23.7)	108.4 (26.6)	<0.001
V/A mental fatigue	149.6 (30.7)	105.5 (38.7)	<0.001
Wessely total fatigue	29.5 (6.4)	15.3 (4.8)	<0.001
SF36 total score	353 (291-415)	643 (576-710)	<0.001
SF36-physical function	45 (35-55)	92 (83-103)	<0.001
SF36-role physical	0 (0-25)	100 (0)	<0.001
SF36-bodily pain	41 (31-52)	84 (74-94)	<0.001
SF36-general health	37 (15)	67 (17)	<0.001
SF36-vitality	25 (15-35)	60 (46-64)	<0.001
SF36-social function	38 (13-63)	100 (84-116)	<0.001
SF36-role emotional	67 (34-101)	100 (83-117)	ns
SF36-mental health	65 (14)	73 (16)	0.05
HAD depression	5.0 (2.5-7.5)	6.5 (2.5-10.5)	ns
HAD anxiety	5.0 (2.1-7.9)	7.0 (3.9-10.1)	ns
PSQI total score	6.0 (4.5-7.5)	5.0 (2.4-7.6)	ns
Barsky amplification	9.5 (3.9)	7.0 (4.4)	0.008

Figure 4.1



Statistically significant differences denoted as follows ~
a, P< 0.05; **b**, P< 0.02; **c**, P,< 0.01; **d**, P< 0.001

Figure 4.2



Statistically significant differences denoted as follows ~
a, P< 0.05; **b**, P< 0.02; **c**, P,< 0.01; **d**, P< 0.001

4.1.2 CFS patients and a sub-group of patients with depressive disorders

A small subgroup of 10 depressed patients was recruited for comparison with the CFS patients on the same measures. Due to the differences in size between groups, t-tests were considered to be more appropriate for this comparison (CFS versus sedentary controls) rather than use of ANOVA to compare all three groups. The ANOVA test would allow us to test the significance of the differences between 3 or more means but as a parametric test it requires normal distributions and acts as a between group and within group variance. It was felt that a total of 10 patients in the depressed group was too small a number to justify the use of this test. Furthermore, the main interest at this stage was to compare the response of the CFS patients and the depressed patients to the given measures. Following on from this thesis, we intend to continue recruitment of this patient group for further analysis.

Table 4.4 Characteristics of CFS patients and patients with depressive disorders

Values are mean (SD) or median (IQR)

Characteristic	CFS Patients (n=66)	Depressed patients (n=10)
Age (years)	37.2 (10.7)	37.1 (10.3)
Height (cms)	169.5 (162.9-176.1)	172.0 (166.1-177.9)
Weight (kgs)	65.0 (53.9-76.1)	72.6 (9.9)
Body Mass Index (kg/m^2)	22.9 (20.2-25.7)	23.6 (20.2-26.6)
Total skinfold (mm)	52.6 (36.8-68.5)	41.5 (22.8-60.1)
Female/male	49/17	6/4

All of the patients with depressive disorders were on medication at the time of assessment. There were no significant differences in the main characteristics of the 10 depressed patients recruited and the CFS patients with respect to age, height, weight, BMI and total skinfold

measurement and, although the gender ratio was 6/4 females to males, this was not statistically significant from the CFS group.

Results on the physiological and symptomatic measures with this group are summarised on Table 4.5. There were no significant differences on any of the physiological measures of peak oxygen uptake, ventilation, heart rate or blood lactate, nor on test duration, recovery heart rate, total RPE or submaximum blood lactate at an RPE of 14.between the depressed and CFS patients. However, there was a tendency in the depressed group towards a higher isometric quadricep strength level although the difference was not significant between the groups. On submaximal measures, oxygen uptake was significantly lower in the depressed patients at 4 ($p=0.02$), 8 ($p=0.004$), 10 ($p=0.05$), 12 ($p=0.05$), 14 ($p=0.003$) and 16 ($p=0.003$) minutes on the treadmill walking test. There were no differences on submaximal heart rate or perceived exertion rating.

Table 4.5. Physiological and symptomatic measures in patients with depressive disorders. Values are mean (SD) or median (IQR).

*** indicates a significantly higher level ($p < 0.05$) compared to the CFS patient group**

 # indicates a significantly lower level ($p < 0.05$) compared to the CFS patient group

Variable	Result	Variable	Result
VO_2 peak ($ml.kg^{-1}.min^{-1}$)	30.6 (7.7)	V/A total fatigue	307.3 (61.1)
VO_2 peak ($l.min^{-1}$)	2.2 (1.9-2.5)	V/A physical fatigue	147.6 (33.0)
Ventilation max ($l.min^{-1}$)	60.8 (48.6-73.4)	V/A mental fatigue	159.8 (32.4)
Heart rate max (BPM)	171 (19)	Wessely total fatigue	33.3 (6.8)
Recovery heart rate (BPM)	111 (26)	SF36 total score	358 (289-427)
Test duration (minutes)	12.3 (4.9)	SF36 physical function	85 (73-98)*
Total RPE	84 (27)	SF36-role physical	50 (62-94)*
Submaximum blood lactate ($mmol.l^{-1}$)	2.5 (2.1-2.9)	SF36-bodily pain	51 (38-64)
Peak blood lactate ($mmol.l^{-1}$)	4.6 (1.9)	SF36-general health	43 (23)
FVC ($l.min^{-1}$)	3.6 (0.6)	SF36-vitality	20 (9-31)
FEV1 ($l.min^{-1}$)	3.0 (0.6)	SF36-social function	38 (22-54)
FEV1/FVC ratio	81 (8)	SF36-role emotional	0 (0-16)#
MVC (Newtons)	420 (128)	SF36-mental health	32 (15)#
		HAD depression	13 (11.3-14.8)*
		HAD anxiety	12 (9.3-14.8)*
		PSQI total score	9 (4-14)
		Barsky amplification	8.3 (3.2)

On the symptomatic measures, the depressed group scored significantly higher on SF36 measures of physical function and role and significantly lower on emotional role and mental health. They also had higher levels of depression and anxiety on the HAD scale.

4.1.3 Discussion of baseline measures (no intervention)

The National Task Force for CFS, PVFS and ME (1994) reports a peak incidence of CFS in the 20 - 40 year age range with a slight female predominance and a strong representation from teachers and the health professions. Previous studies with CFS patients have found a 3 : 1 female to male predominance with a mean age of 32 - 38 years when assessed. The CFS patients recruited into the current study, with a mean age of 37.2 years and a 74 : 26% female to male ratio, were typical of those previously studied. Previously reported illness duration ranged from 6 months to 20 years with a mean of about 47 months (Wessely & Powell, 1989; Wood et al, 1991; Wong et al, 1992; Gibson et al, 1993; White et al, 1995). Those who reported a causal attribution, found a viral illness at onset to be the most frequently cited cause, ranging from 53% (Wood et al, 1991) and 57% (Gibson et al, 1993), 63% (White et al, 1995) to 66-90% (Schleuderberg et al, 1992). Illness duration recorded by the current CFS patients was 37.4 months with a wide range (6 months to 17 years) with 67% (44/66) blaming viruses as the cause. Comparison of the above information with other studies serves to confirm that the current group of CFS patients are typical and similar to previous groups of CFS patients studied, in terms of illness characteristics, age, height, weight and gender distribution. This also indicates the feasibility of applying results from this trial to CFS patients in general.

Examination of the physiological results of the control and CFS patients indicates that the CFS group score significantly lower on all measures of physical fitness when compared to the healthy control group. Careful screening of the control group ensured that those recruited were truly sedentary, in that they rarely or never took part in any strenuous activity, or very infrequently took part in moderate forms of activity. The mean VO_2 peak for the control

group was lower than the control group assessed by Riley et al (1990), who reported a mean peak VO_2 of 37.9 mls.kg.$^{-1}$min^{-1}, a similar maximum heart rate, but a lower peak blood lactate after the test, 5.5 mmol.l^{-1}, which was a somewhat low level for a test of maximum effort. The mean value of 34.1 mls.kg.$^{-1}$min^{-1} measured for VO_2 peak in the controls in the current study was below the expected range, for their age, of 36 - 40 mls.kg.$^{-1}$min^{-1} (McArdle et al, 1994). In spite of this, the low level of exercise tolerance and aerobic capacity was still significantly higher than results recorded in CFS groups. Separating the peak VO_2 levels into those for males and females and comparing them to UK data from the National Fitness Survey (1993) confirms that both groups, CFS patients and the controls, are below the optimum levels (45.5 mls.kg.$^{-1}$min^{-1} for males and 34.8 mls.kg.$^{-1}$min^{-1} for females in the 25-34 year age group), with the CFS being lowest. This would indicate that, in the case of the CFS patients, these individuals tend to reduce, not only general activity/exercise levels to those of sedentary individuals, but must also adapt an even more inactive lifestyle, possibly curtailing normal functions (such as socialising, housework or shopping) in order to control and minimize their fatigue. There were no differences on measures of body fat (total skinfold), body mass index or resting lung functions between the CFS patients and either the healthy sedentary controls or the depressed patients. All of these measures were within normal expected ranges for healthy individuals, i.e. FEV1/FVC ratio greater than 75 %, and body mass index less than 25. Rather than using the total skinfold to estimate the body fat percentage of individuals, this was just used to compare differences in the total millimetre measurement between groups. This limits the margin of error associated with predictions using regression equations. None of the groups has abnormally high total skinfold measurements that would indicate any cause for concern.

Comparing the CFS and control groups on the cardiorespiratory measures, there were no differences between the 2 groups in resting lung function, indicating that there were no abnormalities in the CFS group at rest that would interfere with lung function during exercise. Despite the age similarity in the two groups and, thus, age predicted maximum heart rate, the control group pushed themselves to a significantly higher heart rate than the CFS patients (181 BPM vs 171 BPM). This, and the lower maximum ventilation and peak

exercise heart rate are more in line with an inability to continue exercise to true physiological maximum (91.6% age-predicted maximum heart rate vs 97.6% in controls). Although many factors could affect this, there are two main aspects that are more relevant here. One of these factors is that the strength levels, which are below the level be required for normal functioning, found in these subjects, would cause them to terminate the exercise due to peripheral fatigue in the already weak leg muscles. Another factor is could be their low pain tolerance, which could be a consequence of long periods of inactivity, results in termination of the test at a peak lactate level of only 5.4 $mmol.l^{-1}$ vs 6.7 $mmol.l^{-1}$ in the controls. However, continuation of an exercise test to almost 92% of predicted maximum heart rate does indicate a certain degree of motivation above and beyond just giving up as soon as the exercise became a little uncomfortable. Patients did perceive their effort as maximal at the end of the test, with all patients reaching RPE levels of at least 17, such that it was more likely to be physiological factors, such as weak or fatigued muscles, combined with an inability to discern between normal discomfort due to the exercise and abnormal pain or fatigue, that prevented them from continuing, rather than a lack of motivation or interest. Riley et al (1990) also found a lower peak VO_2 in their group of 13 CFS patients vs. 13 controls (31.8 vs. 37.9 $mls.kg^{-1}.min^{-1}$), and a shorter test duration (11.2 vs. 14.1 minutes) measured on a Bruce test, but no difference in maximal heart rate or peak blood lactate. Both these and the current study results are slightly different to the group of 7 CFS patients studied by Kent-Braun et al (1993), whose mean VO_2 max of 32.5 $mls.kg^{-1}.min^{-1}$ was reached at 98% of predicted maximum heart rate with a higher peak blood lactate of 7.2$mmol.l^{-1}$, but this was a relatively small group with a higher proportion of males.

It must be remembered that it is very difficult for most individuals, other than trained sports people, to push themselves to their maximum physiological capacity, or indeed, to even know when they have reached that level. Therefore, in studies assessing CFS patients and untrained individuals, one would not often observe the criterion blood lactate level of 8 $mmol.l^{-1}$ or a plateau in oxygen uptake values, that are considered as evidence of a true VO_2 max (BASES, 1990). In these studies, it is really a peak VO_2 that is being measured as the individual's perceived functional maximum.

Other studies that measured exercise tolerance in CFS patients compared to controls reported a 2 - 3 minute shorter test duration in the CFS patients on both cycling or walking tests, as was the case in the current study; 10 vs. 12.8 minutes. As in the current study, Gibson et al (1993) also found that CFS patients terminated the test at a heart rate that would be considered to be below their age-predicted maximum HR. This was significantly lower in the CFS patients than in the controls (163 vs. 190 BPM). Montague et al (1989) found that only 13% CFS patients reached target HR (85% age-predicted max) in a cycle test compared to 63% of controls, as previously mentioned. However, age-predicted maximum heart rate is only a rough guide of an individuals true maximum, which may be higher or lower than this level. The CFS patients in the current study terminated the test at 91% of age-predicted maximum heart rate versus 98% in the controls, which is considerably higher than previously recorded in other CFS groups. This was closer to cycle test results with a group of effort syndrome patients, who reached a maximum heart rate of 166 BPM (89% predicted maximum) compared to the 190 BPM (100% maximum) reached by the control group (Stokes et al,. 1988). This is unusual; as untrained individuals tend to terminate a cycle test earlier due to local fatigue in the legs prior to attainment of their cardiovascular maximum.

It could be argued that the fact that the CFS patients reached only 91% of their predicted maximum heart rate, represents a submaximum effort and that they just did not push themselves hard enough. However, a number of factors should be taken into account when considering this. Firstly looking at the RPE levels, whereby all patients rated their exertion level as 17 or above, i.e. maximum levels, at the end of the test, indicates that they did push themselves to the maximum effort that they could achieve. Reaching 91% of the estimated maximum heart rate does take a considerable effort, particularly from a group of individuals who have not only been leading very sedentary lives, as with the controls, but also whose activity level has been reduced to absolute minimum levels, often involving long periods of complete inactivity or rest. In some cases this may have involved being bed-ridden or chair-ridden. It is not surprising that individuals who have had to adapt to this type of lifestyle would find it difficult, in terms of muscle weakness, pain or fatigue to reach their maximum

heart rate, or to have any concept of what a true maximum effort feels like. It could also be expected that deconditioned individuals with low leg strength levels would find it difficult to reach high or maximum levels before leg fatigue or weakness prevents them from continuing with the exercise. It must be pointed out that marathon runners, who also have low leg strength levels, do not have difficulty reaching their cardiovascular maximum. However, they are well-trained individuals and their leg strength, although disproportionate to their high cardiovascular fitness level, is not generally below population norms, as is the case with the CFS patients. Therefore, it is reasonable to assume, that the maximum levels recorded by the CFS patients in this study represent their maximum level in terms of effort and current physical status, which may be different from their true physiological maximum level, but which is hindered by functional limitations resulting from a long-term illness. It is possible that a regular exercise programme may serve to encourage them to push themselves harder and to discover what their body is capable of, while under the supervision of the exercise programme. It must be remembered that many barriers are being confronted here, one of the most important of which is exercise or activity, such that it is only natural for them to be cautious about pushing themselves too hard at the start.

Another measure, which would reflect pain tolerance, is the blood lactate taken once they indicated an RPE level of 14. The CFS patients found the level of exertion to be between "somewhat hard" (RPE =13) and "hard" (RPE =15), when their blood lactate reached a level of 2.8 $mmol.l^{-1}$, whereas the control group reached a lactate level of 3.5 $mmol.l^{-1}$ before they considered that the exercise had reached this perceived level of intensity. This is consistent with speculations about the factors affecting individual perception of exertion, in that local factors such as blood lactate and muscle strain dominate at low to moderate intensities, with central factors dominating at higher intensities (Mihevic, 1981).

Further comparisons can be made during sub-maximal stages of the exercise test. Ability to exert oneself maximally can depend on motivation and familiarity with exercise, whereas measures of physiological demands during sub-maximal exercise are frequently a better indicator of actual functional capacity or training status. This is similar to the strong

correlation between sub-maximal running economy, rather than VO_2 max, and distance running performance (Powers et al, 1983). It is interesting that submaximal oxygen uptake, but not heart rate, at selected stages, was lower in the control group, showing a greater economy of effort in the controls compared to CFS patients. Since a decrease in oxygen utilisation, usually a result of a more efficient oxygen extraction and delivery, is one of the measurable effects of training of a regular exercise programme, the converse could be expected as a result of a lack of exercise or complete inactivity. Although the control group were not regular exercisers, a normal daily lifestyle requires a certain amount of ambulatory activity, which probably becomes very restricted in the lifestyles of those suffering from chronic fatigue syndrome, as they try to conserve their limited energy levels, in order to get through the day. This may also entail extended periods of complete inactivity and sitting or bedrest. Therefore, at an equal intensity of exercise or amount of work, the CFS patients demonstrate a reduced exercise efficiency and a higher demand for oxygen independent of effort involved. This again lends support to the concept that the CFS patients are less physically fit than a group of healthy sedentary individuals.

Differences in perceived exertion throughout the test were significantly lower in the controls than with the CFS patients, indicating a higher feeling of exercise stress at all intensities below maximum. Previous research has shown the RPE during exercise is reduced following a regular training programme (Ekblom & Goldberg, 1971), which would also suggest that, conversely, deconditioning and inactivity would have a negative effect on RPE, leading to an increase in effort perception during exercise. Since the CFS patients had lower than optimal levels of muscle strength and a reduced aerobic capacity, local factors (physical strain on the working muscles) would lead to the increased RPE at lower exercise intensities, while at higher intensities, central factors would dominate (HR, oxygen uptake and ventilation) leading also to a higher RPE in the latter stages of the test, and an earlier rating of maximum RPE levels. This is consistent with research on the factors affecting perception of exertion during exercise (Mihevic, 1981; Pandolf, 1983).

Other exercise studies with CFS patients have also measured this tendency towards a higher perception of exertion at submaximal levels (Riley et al, 1990; Montague et al, 1989), but this was associated with a higher heart rate than in the control group. In contrast to the results in the current study, Riley et al (1990) found a higher heart rate, but not oxygen uptake at submaximum stages in their CFS group compared to healthy controls. They suggested that physical deconditioning could partially account for the excess fatigue and deficient cardiovascular response, but also speculated that sleep disturbance could alter the sensory threshold for pain afferents coming from the active muscles and joints, leading to the greater perception of effort. However, in the current study we also found higher RPE levels throughout the walking test, despite no disturbances in sleep, and is therefore unlikely to be the sole explanation. Montague et al (1989) also found abnormally high RPE rating, as well as heart rates, in relation to workload in a group of 41CFS patients. Only 33% of these patients reached their target heart rate compared to 66% of controls. The higher submaximal oxygen uptake measured in the current study agrees with the findings of Wagenmakers et al (1988) of a high exercise stress at low exercise intensities and potentially an increased dependence on glycolysis. These could all be considered as predicted adaptations to reduced habitual activity, which appears to be the case in a large proportion of CFS patients. Therefore, we can see that perceived effort rating is consistently high at submaximal exercise intensities in all studies of exercise tests with CFS patients. However, pure physiological responses, as opposed to RPE as a psychophysiological measure, tended to show varied results between normal or slightly raised heart rates and oxygen uptake levels, and it would be difficult to determine whether the peripheral effect, i.e. a dysfunction in the working skeletal muscle, was greater than the cardiac effect in reducing exercise capacity in these patients, since inactivity and deconditioning will have an effect on both.

The same measure of isometric quadriceps strength was included in the 1991 National Fitness Survey (1992) and an optimum of 75% of body weight was set as the ideal level for knee extensor isometric strength, with the lower limit of normal defined as 50% of body weight. If peak force is less than 50%, the individual will find it difficult to support the full body weight with both feet on the ground and rising from sitting unaided becomes difficult. This is

based on original standards set by Edwards et al (1977), who recommended that an adult's predicted "normal" MVC (in kg force) is about 75% of their body weight and the lower limit of normal is approximately half their body weight (regression equation: y (MVC) = 7.91 x (weight) - 3.77). The MVC for the sedentary controls almost reached the 75% body weight (485 Newtons), whereas the CFS patients were only just above the minimum level of 50% body weight (325 Newtons), implying that they would have difficulty with activities, such as climbing stairs, as was frequently reported by them. Gibson et al (1993), also measured quadriceps isometric strength in a group of 12 CFS patients compared to matched controls, and found only small and non-significant differences between groups (443N vs 476N), although individuals did show a weakness related to body weight and a positive response to twitch interpolation, even though 60% of patients attained an MVC without twitch. However, the CFS patient group studied were 50% male, which may explain their results being somewhat higher than those of the current study.

Rutherford and White (1991) and Stokes et al (1988) also used the same measure of strength with smaller groups of CFS patients, and found that differences compared to controls were not significant, and those who did not produce a maximal effort voluntarily, reached normal ranges with twitch interpolation. They suggested that this indicated a submaximal effort, rather than any intrinsic weakness. The highest force recorded out of the 5 trials was taken as the MVC for each subject and for 65% of the CFS patients this highest effort was on a trial without stimulation, compared to 80% of controls. This difference between the two groups is not significant. This would indicate that a large proportion of the CFS patients were not subject to a central inhibition that prevented them from producing a maximal contraction, that could be overcome by artificially stimulating a greater proportion of the muscle. It must be pointed out that, due to limitations in the equipment available, the use of the twitch interpolation technique in the current study lacked in its ability to determine the amount of extra force added by the twitch, as was explained in the methods. Interestingly, 20% of the control group reached their highest level recorded on a trial with stimulation of the muscle implying that a moderate amount of normally active individuals, in terms of lifestyle, may not be able to fully activate their muscle. This MVC level reached in CFS patients, with or

without stimulation, was still below the expected range for their body mass. In their review, Edwards et al (1993), found that most patients examined, who had effort syndromes, post-viral fatigue or CFS, had been able to generate normal force using several different muscle groups, with or without verbal encouragement, and that those who could not, did so with twitch interpolation. The increased force produced on stimulation implies that central factors, such as low motivation or fear of pain, could be the cause of low recorded strength levels in some patients. However, the fact 65% of the CFS patients in the current trial, whose highest level was reached on an unstimulated trial, did not indicate a lack of motivation.

The detrimental effect of inactivity on cardiovascular capacity has already been well documented and discussed, but it is also true that inactivity has negative effects on strength. Indeed, Kottke (1966), proposed that, if maximum tension exerted each day is less than 20% of the maximal strength of the muscle, then strength decreases, and when no tension is exerted throughout the day, loss of strength occurs at a rate of approximately 3% per day. Reports from patients in this and other studies suggest that many of them do considerably reduce the time spent on their feet, sometimes reverting to bedrest, so that significant losses in muscle strength would be expected. The measured low aerobic capacity and muscle weakness were most likely responsible for the shorter test duration in the CFS patients, both or either of which would prevent them from continuing the exercise. Smith et al (1996), found a mean isometric leg extension in a group of 81 - 90 year old women to be 217N which again was below the 50% of body mass level (289N) that would be required for normal and independent function. More interestingly, they found a positive correlation between this measure and walking speed, functional reach and ability to reach varied and increasing step heights. These functional activities, which the current group of CFS patients also expressed difficulties with, could, at least partly, be attributable to their below optimum leg strength. Therefore, speculations on the underlying mechanism responsible for the low functional capacity and strength measured in selected groups of CFS patients compared to healthy controls, have varied from peripheral fatigue (Montague et al, 1989) to central/effort perception (Gibson et al, 1993; Riley et al, 1990), with little general agreement and evidence for both. With the added data, it would be reasonable to accept that there is a contribution

from both since both are susceptible to the detrimental effects of detraining or inactivity, and the CFS patients studied were both unfit and weak.

Symptomatic measures

As would be expected there were significant differences between the CFS patients and the sedentary controls on all measures of both physical and mental fatigue since this is the primary complaint with this condition. Similarly, other measures indicative of this symptom are physical function, vitality and physical role scores on the SF36 scale, all of which were significantly reduced in the CFS group. It appears also the overall feelings of increased and abnormal physical fatigue has a consequential effect on social function, general, and mental health. It is probable that sufferers are forced to curtail their normal social activities due to fatigue and this loss of social contact and in some cases, a feeling of isolation, leads to the decrease in general health perceptions, frustration and stress. Without the distraction from regular social contact, an individual with such symptoms as muscle weakness, pain and fatigue may then tend to focus unnecessarily or excessively on these sensations, which could increase their fear and frustration even more. A significant intergroup difference in the Barsky amplification score was found, which is indicative of a heightened awareness of, or increased tendency to amplify bodily symptoms and is actually influenced by disruption of daily social or other routines (Barsky et al, 1988). There were no differences between groups on the HAD depression and anxiety scores, neither of which reached case level, since those with psychiatric disorders were excluded prior to entry. However, the lower scores on the SF36 mental health scale in the CFS group, indicated that, although not necessarily clinically depressed, they felt downhearted, low, unhappy and nervous. The reduced scores on these scales measuring physical, mental and social function were also not due to sleep disturbances since those with significant sleep disorders were excluded prior to testing, confirmed by the similarity between the groups in the Pittsburgh sleep quality score.

Therefore, the profile that emerges of the CFS patients is of a group of individuals who are not clinically depressed but who are suffering the psychological side effects of continued and prolonged fatigue. The longer this illness continues, it must be true, that the effects of this on

social function and lifestyle become worse, which would ultimately be linked to a low perception of their general health and a loss of self-esteem.

CFS patients compared to depressed patients

We chose to examine any similarities and differences on both the physiological measures on CFS patients with a small group of depressed patients, since CFS can and has been diagnosed as purely a depressive illness. The depressed patients were not offered any exercise treatment. There has been a relatively small number of studies on the physiological capacity of patients suffering from depression, but generally, patients, with either anxiety or depressive disorders are less fit than the general population and, this is usually due to inactivity (Martinsen, 1990). Similarly the depressed patients in the present study, although only a small group, had low fitness levels, comparable to those of the CFS patients on measures of maximum aerobic capacity, exercise tolerance and strength. We did not record activity levels in the depressed group of patients, but results of a recent unpublished ambulatory study with CFS patients revealed that they do have significantly lower activity levels than sedentary controls (Dash, personal communication). Taking this into account, it would appear that depressed patients also have similarly low daily levels of activity, which is consistent with their low fitness levels. However, the differences on some of the symptomatic measures reveal that the depressed patients perceive that they can do more physically, and they do not see themselves as having a reduced or restricted physical function. The CFS patients, on the other hand, perceive that they are restricted physically and therefore, avoid activity as the feared stimulus that could worsen symptoms. The low scores of mental and emotional health and the high scores on the HAD scale in the depressed group, could reveal more of a mental than physical restriction to them being more active, due to lack of interest or motivation.

This puts forward a strong argument for the use of exercise in treatment programmes with these patients (Martinsen, 1993), since the psychological benefits of regular exercise have been previously well documented (see review section 2.4.1). Martinsen (1990) assessed the physiological capacity on a group of 90 depressed patients and found that they had normal, or

slightly higher than predicted values for resting lung function, but lower than predicted values for VO_2 max and physical working capacity, indicating that they had no restrictions to exercise other than a lack of fitness. They stopped before reaching age-predicted maximum heart rate, but reached a peak RPE of 18 and peak blood lactate of 10mmol.l^{-1}. Similarly, the depressed patients in the current study recorded significantly lower levels for VO_2 peak, (when compared to either US or UK norms, as discussed previously). They continued the walking test to similar high RPE levels as the CFS group with the same, relatively low, peak blood lactate levels, which was considerably lower that peak blood lactate levels measured by Martinsen (1990). The depressed patients, on the whole, appear to be equally as unfit or deconditioned as the CFS patients, implying that they also restrict their activity levels, possibly for different reasons. They choose not to exercise, with lack of motivation and depressed mood having a significant effect. However, they do not perceive that they have any physical restrictions to participation in activity and this sets them apart from the CFS patients.

It is interesting that the depressed group of patients showed a tendency towards higher values and greater leg strength than the CFS group. Many CFS patients become bedridden at various stages of the illness, and this may be responsible for the low levels of strength, whereas individuals suffering from depression, although not very physically active, may be less inclined to spend such extended periods in bed. This may also explain why they had a better submaximal exercise tolerance with significantly lower oxygen uptake levels on all stages of the walking test.

The fact that there were similarities in the physiological results between the CFS and depressed patients, but that there were considerable differences in the symptomatic/psychiatric measures, reveals a clear distinction between the two groups. This suggests that the fatigue, low fitness level, and poor exercise tolerance of CFS patients are most likely due to reduced activity levels. This fatigue is not just due to depression and poor motivation or lack of interest in the activity, as there are significant differences on measures of mood and mental health compared to depressed patients. Fatigue associated with

depression (mainly mental fatigue) would be expected to be different than the extreme physical fatigue and weakness associated with CFS. Restriction of daily living activities can be a cause and a consequence of a depressive illness and may have important consequences.

The current results are similar to those of pure (not yet chronic) fatigue syndrome patients measured 6 months after upper respiratory tract infections (White et al, 1995b). Those with fatigue syndrome, in the absence of psychiatric disorder, had greater physical fatigue and felt socially incapacitated compared to healthy controls. However, their total scores on the visual-analogue scale of 239 was somewhat better that the 318 found with the chronic fatigue group, indicating that the longer duration of a fatigue syndrome is likely to worsen this symptom. They also separated out those with psychiatric disorders, found no differences in the HAD depression and anxiety scores, between fatigue syndrome and controls, as in this study. Few other studies with CFS patients excluded those with psychiatric disorders such that it is difficult to delineate those with pure fatigue syndrome from those with fatigue that can be a consequence of psychiatric disorders. Exclusion of those with psychiatric disorders enabled the examination of the effects of the fatigue syndrome itself on physical, mental and social function.

Kottke (1966) suggested that the immediate emotional response to limitation of activity, is similar to that in other situations of stress, and can lead to a person showing traits of insecurity, anxiety and dependency. Therefore, in the long-term, as activity is further reduced and the condition becomes chronic, emotional problems could be expected to worsen. Anxiety, hostility, tension, complaints of discomfort and changes in pattern of sleep also occur depending on the personality of the individual, particularly as they are forced to rely on others for simple tasks, then independence and self-esteem decrease.

These results indicate that there are clear and significant differences on all measures of fatigue, which appear to have effects on other psychological symptoms, but are independent of the effects of depression, anxiety or other psychiatric disorders. Poor mental and general health in CFS patients could also have an effect on sufferers ability to cope with the long term

effects and their ability or motivation to seek treatment, particularly any form of physical treatment.

4.1.4 Summary

This baseline study which has assessed both physiological and psychological parameters in a large group of CFS patients confirms, and adds to, previous results on smaller groups. These revealed a decreased aerobic capacity, a reduced exercise tolerance, generally associated with an inability to continue to physiological maximum capacity and an increased perception of exercise at submaximal levels. Contrary to other studies, a low maximum isometric quadriceps strength was also measured. This is the case when compared to either a sedentary control group or expected normal ranges. In addition, the CFS patients differed from healthy, non-fatigued individuals on all symptomatic measures of physical and mental fatigue and function, and social function which was not a result of a psychiatric disorder. However, they were no different from depressed patients on all physiological measures, representative of another patient group with very low reported activity levels, but the differences between these two groups on certain psychological measures, again confirms that this fatigue is not just as a result of depression. However, the CFS patients, in contrast to the depressed group, have more of a perceptual problem of low functional capacity and physical restrictions that could cause them to reduce their activity levels. It is plausible that much of the reduced physiological capacity and exercise tolerance are a consequence of the inactive lifestyles adopted by these patients, due to perceived physical restrictions, resulting in physical deconditioning. This is also associated with a fear of persevering with any form of activity that might be harmful or lead to a relapse. If this fatigue is largely centrally mediated, as Edwards et al (1993) have suggested, then the importance of perceptual, and possibly other psychological factors in perpetuating this condition, cannot be ignored. As discussed, exercise has been used successfully in the treatment of several chronic conditions as well as depression and anxiety, and these results would justify the case for a trial of graded exercise therapy with this group of CFS patients, with a view to improving both physiological and psychological symptoms.

4.2 Examination of physiological and symptomatic treatment effects

4.2.1 Between groups: exercise vs flexibility and relaxation at baseline

The main characteristics of the two subject groups are given in table 1. Subjects randomly allocated to either the exercise or flexibility treatment groups were well matched for age, height, weight and gender but subjects in the exercise group had a significantly longer duration of illness (p=0.03) (Table 4.6).

Table 4.6. CFS patient characteristics at baseline. All results are mean (SD) or median (IQR), n (%). * indicates a significant difference between groups (p<0.05); comparisons otherwise are not significantly different

Characteristic	Exercise Group (n=33)	Flexibility Group (n=33)
Age (years)	37.9 (9.3)	36.6 (12.0)
Height (cms)	169.5 (7.6)	168.4 (7.3)
Weight (kgs)	69.2 (18.3)	67.3 (12.1)
Body Mass Index (kg/m^2)	23.9 (5.1)	23.7 (4.1)
Total skinfold (mm)	55.6 (22.6)	61.6 (22.6)
Illness duration (years)	3.8 (2.4 - 3.2)	2.0 (0.8 - 3.2)*
Female/male	23/10	26/7
Smokers	5 (15%)	6 (18%)

All patients were asked several standard questions with regard to lifestyle and habits at the initial assessment session (baseline). Fifteen and eighteen per cent of the exercise and flexibility group, respectively, smoked. Sixty four percent (21) and 49% (16) from the

exercise and flexibility group, respectively, considered themselves regular exercisers prior to the onset of the illness. The most frequent activities were walking, swimming, aerobics/gym work, tennis and cycling. With regard to those working or studying, in the exercise group 8 were working full-time, 4 part-time and in the flexibility group 5 were still working full-time and 8 part-time. The remainder, 21 (32%) and 20 (30%) in the exercise and flexibility group, respectively, had given up work or study completely, due to the illness.

Fifteen (45%) of the subjects in the exercise group were taking medication, 8 were taking full-dose antidepressants, 5 were taking antidepressants at hypnotic doses at night and 2 were on other medication (anti-convulsant or HRT). In the flexibility group, 17 (51%) were on medication, 12 were taking full-dose antidepressant drugs and 5 were on antidepressants at hypnotic doses. There were no significant differences between the groups in type and number on medication. Subjects were told to maintain any medications unchanged throughout the six or nine months of treatment and follow-up.

Viral illnesses were the most common subjects' attribution of cause, with 9 out of 66 patients believing the cause to be glandular fever, and 35 blaming other viruses. Other perceived causes were vaccination (2/66), other infections (8/66), miscellaneous (5/66) (nerve palsy, post-natal haemorrhage, severe vomiting, generalised fatigue, recent divorce) and 7/66 did not identify any cause. There were no significant differences between groups in cause attribution.

The physiological test results at baseline for the two groups are presented in Table 4.7. No significant differences were observed in any measures of cardiovascular capacity or exercise response between groups. The FEV1/FVC ratio was a slightly higher in the flexibility group, but mean values for both groups were within normal ranges (ie. >75%) for this variable. Mean maximum aerobic capacity (VO_2 peak) was below the average range for both groups for this age group in the general population (McArdle et al, 1994). Taking the male and female results separately, since about 2/3 of both groups were female, gave a mean of 36.1 (8.0) and 29.7 (6.4) $ml.kg^{-1}.min^{-1}$ for males and females, respectively, in the exercise

group. Values in the flexibility group were 39.4 (8.5) $ml.kg^{-1}.min^{-1}$ for males and 27.0 (7.3) $ml.kg^{-1}.min^{-1}$ for females. Therefore it was mainly the females in both subject groups who were below the expected range for females between 30 - 39 years, of 34 - 38 $ml.kg^{-1}.min^{-1}$. The males in the study group were within (flexibility) or marginally below (exercise group) the normal range of 38 - 42 $mls.kg^{-1}.min^{-1}$. Results from the National Fitness Survey (1992) reported a mean VO_2 max of 34.2 for females and 45.5 for males in the 35 - 44 age group, indicating that both males and females measured were also below the UK population norms.

Table 4.7. Physiological variables of both groups at baseline.

Values are mean (SD) or median (IQR); p> 0.05 is not significant (ns)

Variables	Exercise Group (n=33)	Flexibility Group (n=33)	Significance
VO_2 peak ($ml.kg^{-1}.min^{-1}$)	31.8 (26.8-36.8)	28.2 (23.4-33.1)	ns
VO_2 peak ($l.min^{-1}$)	1.9 (1.4-2.4)	1.9 (1.6-2.2)	ns
Ventilation max ($l.min^{-1}$)	71.2 (52.6-89.7)	68.7 (62.0-77.5)	ns
Heart rate max (BPM)	170 (18)	171 (19)	ns
Recovery heart rate (BPM)	109 (18)	111 (17)	ns
Test duration(minutes)	10.5 (3.7)	9.5 (3.6)	ns
Total RPE	73 (21)	64 (21)	ns
Submaximum blood lactate ($mmol.l^{-1}$)	2.6 (1.4-3.8)	2.3 (1.4-3.4)	ns
Peak blood lactate ($mmol.l^{-1}$)	4.9 (1.9)	5.8 (2.5)	ns
FVC ($l.min^{-1}$)	3.9 (0.8)	3.9 (0.7)	ns
FEV1 ($l.min^{-1}$)	3.0 (0.7)	3.2 (0.6)	ns
FEV1/FVC ratio	77 (9)	83 (5)	p=0.05
MVC (Newtons)	339 (144)	340 (105)	ns

All patients continued the walking test until they reached their perceived maximum capacity, which occurred at 91 (8%) and 92 (9%) of their age predicted maximum heart rate in the exercise and flexibility group, respectively. The test duration at baseline ranged from 2.5 minutes to 20 minutes. The mean duration of 10.5(3.7) and 9.5(3.6) minutes was reached at

a gradient of 12.5% and 10% on the treadmill in the exercise and flexibility group, respectively.

With verbal encouragement 61% (20/33) of subjects in the exercise group and 67% (22/33) of patients in the flexibility group produced a maximum isometric contraction without twitch interpolation, which was applied an two of the five trials. As an observation the peak MVC was recorded on the first trial in a large proportion of the patients. The total RPE score was taken as the sum of each RPE rating indicated by the patients at the end of each stage of the walking test and there were no significant differences between groups. The slightly higher RPE (73 (21) vs 64 (21)) in the exercise group was due to a longer exercise time in this group (10.5 (3.7) vs 9.5 (3.6) minutes), but these differences did not reach statistical significance. When RPE was analysed as the total score divided by the test duration, the baseline values, 7.3 (1.3) (exercise) and 6.9 (0.9) (flexibility), were similar between groups.

Self-reported symptomatic measures (Table 4.8) revealed significant differences only in total physical fatigue as measured by the visual analogue fatigue scale (combining exertional physical fatigue and persistent physical fatigue) and vitality on the SF36. There were no significant differences in total fatigue, perceived physical or functional capacity or other symptomatic measures.

Table 4.8. Symptomatic variables in both groups at baseline. Values are mean (SD) or median (IQR); p>0.5 is not significant

Variable	Exercise Group (n=33)	Flexibility Group (n=33)	Significance
V/A total fatigue	312.1 (49.6)	324.6 (45.0)	ns
V/A physical fatigue	161.1 (27.7)	176.5 (16.4)	p=0.02
V/A mental fatigue	151.0 (26.0)	148.1 (34.3)	ns
Wessely total fatigue	28.8 (7.1)	30.5 (5.6)	ns
SF36 total score	341 (84)	336 (73)	ns
SF36-physical function	48 (22)	46 (18)	ns
SF36-role physical	0 (0-25)	0 (0-25)	ns
SF36-bodily pain	41 (30-51)	41 (30-52)	ns
SF36-general health	39 (14)	37 (16)	ns
SF36-vitality	37 (25-50)	22 (17-28)	p=0.03
SF36-social function	42 (28)	38 (24)	ns
SF36-role emotional	52 (61-98)	84 (50-117)	ns
SF36-mental health	69 (60-78)	64 (60-68))	ns
HAD depression	5.0 (1.5-8.5)	5.0 (2.5-7.5)	ns
HAD anxiety	5.8 (3.6)	5.7 (4.0)	ns
PSQI total score	6.4 (2.4)	6.5 (3.5)	ns
Barsky amplification	9.0 (3.9)	9.7 (3.6)	ns

4.2.2 Between groups : exercise vs flexibility and relaxation after treatment

The main outcome measure, the self-rated clinical global impression (CGI) scores, of subjects completing the study is shown in Table 4.9. As can be seen, 55% (16/29) of those receiving the exercise treatment rated themselves "much better" or "very much better" (CGI 1 and 2 combined) compared to 8/30 (27%) of the flexibility group (Yeats continuity correction = 3.9, 1 DF, p=0.03). Twenty-four per cent more of the exercise group subjects rated themselves "very much better", which was significant (95% ci = 5, 43%). Four subjects in the exercise group and three in the flexibility group did not complete the 12 weeks of treatment. In the exercise group, reasons given included: a friend dying, financial crisis, ovarian cystectomy and felt worse due to corroborated depressive illness. In the flexibility group reasons given included treatment making her worse and two subjects gave no reason for non-attendance at sessions.

Table 4.9. Self-rated CGI change score after completing exercise or flexibility treatment

Rating score	Exercise (n = 29)(%)	Flexibility (n = 30)(%)
1: very much better	9 (31)	2 (7)
2: much better	7 (24)	6 (20)
3: a little better	11 (37)	18 (60)
4: no change	1 (3)	3 (10)
5: a little worse	1 (3)	0
6: much worse	0	1 (3)
7: very much worse	0	0

Analysing by intention to treat 52% (17/33) improved in the exercise treatment group, compared with 27% (9/33) in the flexibility group, (Yeats continuity correction = 4.06, 1

DF, p=0.04; analysing all 33 in each group) (Table 4.10). Intention to treat analysis is useful to identify how many of the patients could be effectively treated with the intervention and includes all patients who started the treatment, in the analysis. A negative outcome, i.e. no improvement, is accepted for those who dropped out, whose results are not available. Only one subject in each group rated themselves worse after treatment; both were suffering from a major depressive illness when re-assessed after treatment.

Table 4.10. Self-rated CGI change score with intention to treat

CGI Score	Exercise Group (n=33)	Flexibility Group (n=33)
1 or 2	17 (52%)	9 (27%)
3 - 7	16 (48%)	24 (73%)

Yeats Continuity Correction = 3.1, 1 DF, p=0.04

A comparison of the physiological parameters in the two groups following 12 weeks of treatment are shown in Table 4.11. There were greater improvements with exercise in both absolute ($p<0.05$) and relative VO_2 peak and maximum minute ventilation ($p<0.05$), indicated by the significant intergroup differences on retest. Test duration tended to be greater in the exercise group ($p=0.08$) and total RPE tended, as a consequence, to be less in the flexibility group ($p=0.07$). When this measure was analysed as RPE total divided by test duration, no significant difference was observed between groups at baseline or post treatment. However a greater per cent change was seen in the exercise group, where the RPE/test duration decreased by 26% (7.3 vs 5.5), compared to a 21% decrease in the flexibility group (6.9 vs 5.4), but this did not reach statistical significance.

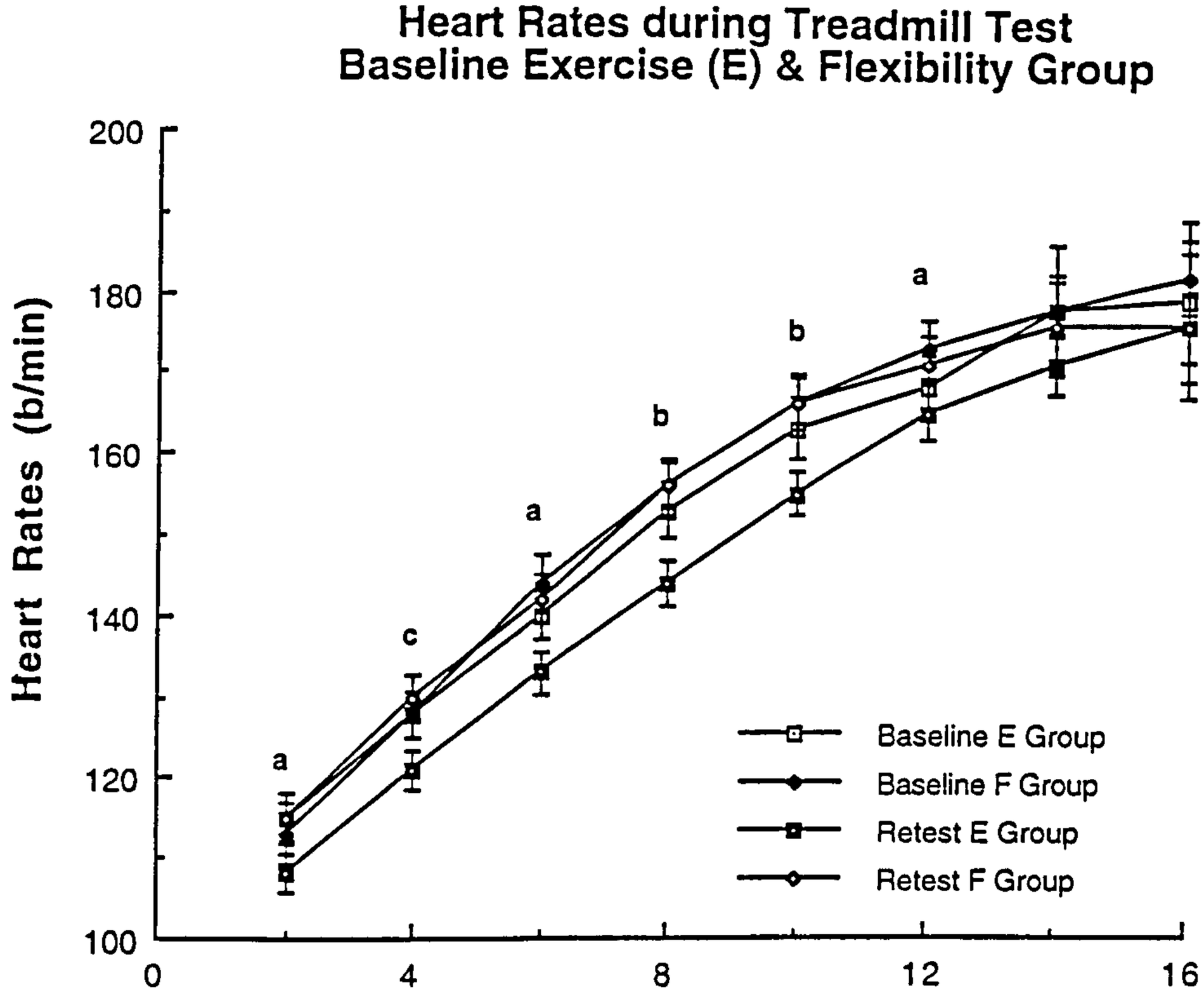
Submaximal heart rate and RPE recorded at each stage of the treadmill test are shown in Figures 4.3 and 4.4, respectively, for the post-treatment conditions. Since there were no differences between the groups at baseline this data is not shown for reasons of clarity There were no significant differences at baseline between the groups for heart rate and RPE,

whereas heart rate at 4 (p=0.04), 6 (p=0.04), 8 (p=0.01), 10 (p=0.002) and 12 (0.04) minutes, and RPE at 6 (p=0.03) and 8 (p=0.005), 10 (0.003) and 12 (p=0.02) minutes were significantly reduced in the exercise group compared to the flexibility group on test 2. We compared submaximal cardiovascular response to exercise between exercise and flexibility groups at baseline and after 3 months by comparing the area under the curve for heart rate versus treadmill stage reached. Peak heart rate did not differ between the 2 groups, but cardiovascular response to submaximal exercise was lower in those who had followed the exercise programme compared to the flexibility group. Mean heart rate per test stage between 6 and 12 minutes was 149 (14) beats.min^{-1} in the exercise group versus 157 (14) beats.min^{-1} in the flexibility group (t=-2.17, 57df, p=0.03). The same analysis of area under the curve for RPE at submaximal levels (6, 8, 10 and 12 minutes) showed a greater reduction in perceived effort in the exercise group in test 2 (t=-2.06, 55 df, p=0.04)

Table 4.11. Physiological variables in both groups after 3 months of aerobic exercise or flexibility and relaxation. Values are mean (SD) or median (IQR). p>0.05 is non-significant but p<1.0 are shown to show a tendency towards significance.

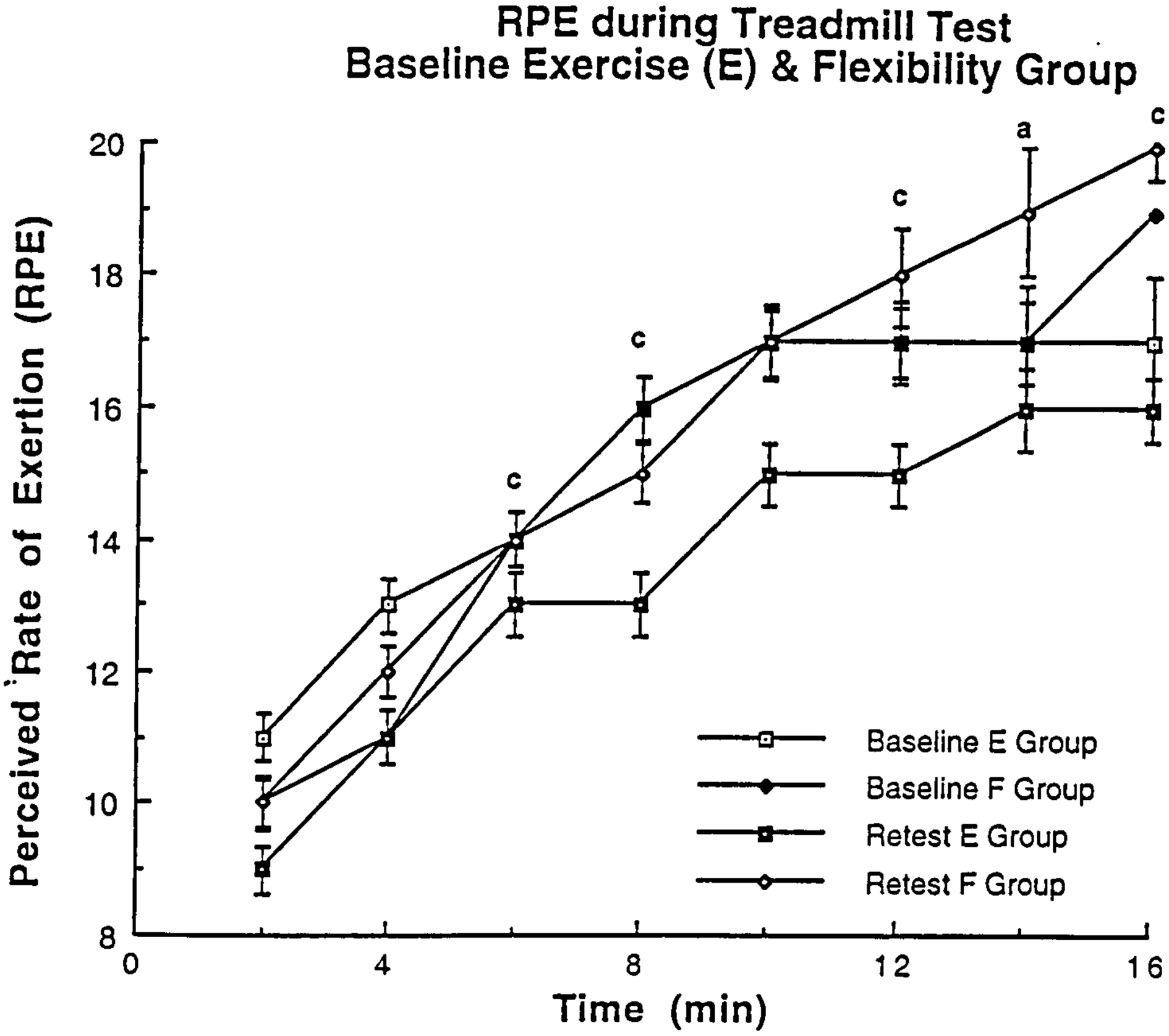
Variable	Exercise group (n=29)	Flexibility group (n=30)	Significance
VO_2 peak ($mls.kg^{-1}.min^{-1}$)	35.8 (30.8-40.7)	29.2 (25.1-35.4)	p=0.03
VO_2 peak ($l.min^{-1}$)	2.2 (1.6-2.8)	1.9 (1.6-2.2)	p=0.05
Ventilation max ($l.min^{-1}$)	88.6(67-110)	76.1 (64-88)	p=0.04
Heart rate max (BPM)	174 (17)	178 (14)	ns
Recovery heart rate (BPM)	111 (16)	115 (15)	ns
Test duration(minutes)	12.5 (3.5)	11.0 (3.3)	p=0.08
Total RPE	68 (18)	52 (24)	p=0.07
Submaxium blood lactate ($mmol.l^{-1}$)	2.0 (1.2-2.8)	2.5 (1.6-3.4)	ns
Peak blood lactate ($mmol.l^{-1}$)	6.2 (2.5)	6.2 (2.5)	ns
FVC ($l.min^{-1}$)	4.0 (0.9)	3.9 (0.7)	ns
FEV1 ($l.min^{-1}$)	3.1 (0.8)	3.2 (0.5)	ns
FEV1/FVC ratio	78(9)	82 (4)	p=0.07
MVC (Newtons)	430 (182)	378 (106)	ns

Figure 4.3



Statistically significant differences denoted as follows ~
a, P< 0.05; **b**, P< 0.02; **c**, P,< 0.01; **d**, P< 0.001

Figure 4.4



Statistically significant differences denoted as follows ~
a, P< 0.05; **b**, P< 0.02; **c**, P,< 0.01; **d**, P< 0.001

Results of the self-reported symptomatic measures are presented in Table 4.12. Fatigue, as measured by the visual analogue total and mental fatigue scales, and Wessely fatigue scores, was significantly lower with exercise. Perceived physical function and general health, were better in the exercise group, with a trend towards improved physical role (SF36 scale) and a significantly greater increase in the SF36 total score. Since the flexibility group were more physically fatigued at baseline, we calculated the percent change and showed that exercise improved visual analogue scale physical fatigue by 19% (flexibility 12%), but the percent differences were not significant. Because the subjects in the flexibility group were more physically fatigued before treatment and had a longer illness duration, we used analysis of covariance and found that neither baseline physical fatigue (Beta= -0.05, t=-0.37, p=0.71) nor illness duration (Beta=-0.10, t=-0.72, p=0.47) covaried with response to treatment.

Table 4.12. Symptomatic variables in both groups after 3 months of aerobic exercise or flexibility and relaxation. Values are mean (SD) or median (IQR). p>0.05 is non-significant but p<1.0 are shown to show a tendency towards significance.

Variable	Exercise group (n=29)	Flexibility group (n=30)	Significance
V/A total fatigue	253.3 (47.6)	286.0 (67.1)	p=0.004
V/A physical fatigue	130.0 (27.6)	153.7 (34.0)	p=0.006
V/A mental fatigue	123.7 (30.9)	132.1 (39.3)	ns
Wessely fatigue	20.5 (8.9)	27.4 (7.4)	p=0.004
SF36 total score	479 (113)	420 (120)	p=0.05
SF36-physical function	69 (18)	55 (21)	p=0.01
SF36-role physical	25 (0-50)	0 (0-25))	p=0.08
SF36-bodily pain	65 (20)	54 (25)	ns
SF36-general health	46 (31-61)	40 (25-55)	p=0.03
SF36-vitality	47 (31-63)	40 (25-55)	ns
SF36-social function	65 (25)	56 (24)	ns
SF36-role emotional	100 (84-117)	100 (67-134)	ns
SF36-mental health	76 (65-87)	76 (64-88)	ns
HAD depression	5.5 (2.9-8.1)	4.0 (0.6-7.4)	ns
HAD anxiety	5.5 (3.0-8.0)	7.0 (3.5-10.5)	ns
PSQI total score	5.0 (3.5-6.5)	6.0 (4.1-7.9)	ns
Barsky amplification	8.4 (3.4)	8.5 (4.1)	ns

4.2.3 Changes within groups with treatment

Analysing the data in Tables 4.7 and 4.8 (baseline) and Tables 4.11 and 4.12 shows that there were changes in physiological measurements within both groups, but aerobic capacity as measured by peak VO_2 only improved significantly ($p<0.04$) in the exercise group (by 13% from 31.8 to 35.8 mls.kg^{-1}min^{-1}). Improvements were observed in both symptomatic and functional capacity after both treatments, but the greatest improvements occurred with those receiving the exercise treatment. Results for each group were compared separately for improvement on each treatment. After the 12 weeks of graded aerobic exercise, significant positive differences were observed in VO_2 peak, both relative ($p=0.001$) and absolute ($p=0.0003$), maximum ventilation ($p=0.0002$), test duration ($p=0.0002$), MVC ($p<0.0001$), blood lactate at an RPE of 14 ($p=0.001$)(the same test stage at the original RPE of 14) and total RPE score ($p<0.0001$). Significant changes ($p<0.05$) were observed in all of the symptomatic measures of physical capacity and fatigue except the HAD depression and anxiety scores, total Pittsburgh sleep score, mental health (SF36) and the Barsky amplification score. Subjects in the flexibility group also showed increases in maximum ventilation ($p=0.001$), heart rate maximum ($p=0.004$), test duration ($p=0.0001$), MVC ($p=0.001$), total RPE score ($p<0.001$) and both blood lactate at an RPE of 14 ($p=0.006$) and post-test blood lactate ($p=0.002$). Symptomatic improvements were observed in total fatigue ($p=0.02$) and physical fatigue ($p=0.004$) (V/A scale), Wessley physical ($p=0.02$) and mental fatigue ($p=0.01$) and SF36 vitality ($p=0.008$), social function ($p=0.02$) and mental health ($p=0.03$). Larger changes were measured following the exercise treatment compared to the flexibility treatment.

Cross-over group

Twenty three subjects who began with the flexibility treatment crossed over to the exercise treatment after 12 weeks of flexibility and relaxation and followed the same exercise programme as the exercise group. Seven subjects chose not to go on to the exercise treatment, mainly because of domestic commitments. Results of this group were compared to baseline parameters measured on entry into the study. Tables 4.13 and 4.14 show the post-exercise data for the flexibility group.

On the CGI score 55% (12/22) of patients rated themselves "much better" or "very much better" (CGI 1/2), after the exercise treatment and compared to baseline. This was not significantly different ($p=0.09$) to the 27 per cent of this group who had improved following the flexibility treatment alone. One patient did not complete the exercise programme due to a foot operation.

Significant increases were measured in absolute and relative VO_2 peak, maximum ventilation, heart rate maximum, total RPE score, test duration, post-test peak blood lactate, MVC with a tendency towards a decrease in blood lactate at an RPE of 14 ($p=0.09$), compared to baseline values. Highly significant changes were observed at all submaximal levels of the walking test on heart rate, at 6 mins ($p=0.008$), 8 mins ($p=0.003$), 10 mins ($p=0.001$) and 12 mins ($p=0.002$) and in RPE scores at 6 mins ($p=0.000$), 8 mins ($p=0.004$), 10 mins ($p=0.04$) and 12 mins ($p=0.02$), versus baseline. In the symptomatic measurements a significant improvement was observed in physical and mental and total fatigue (V/A scale), Wessely fatigue, physical and social function and general health as measured by the SF 36, Barsky amplification with a tendency towards increased vitality ($p=0.09$). In addition to the increases observed after the flexibility programme, new significant improvements from baseline were observed in VO_2 peak, strength, physical function and physical fatigue.

The post-exercise results of the cross-over group were also compared to the measures recorded after the 12 weeks of flexibility and relaxation, on all variables, i.e. post-flexibility versus post-exercise. This was in order to compare the amount of change resulting from the different treatments in the same group of subjects. To avoid complication, these results tables are presented in Appendix E and is discussed on page later.

Variable	Baseline (n=33)	Post exercise treatment (n=23)	Significance vs baseline	3 month follow-up (n=20)	Significance vs baseline
VO_2 peak ($ml.kg^{-1}.min^{-1}$)	28.2 (23.4-33.0)	31.5 (27.2-35.9)	(0.06)	28.5 (20.1-36.9)	ns
VO_2 peak ($l.min^{-1}$)	1.9 (1.6-2.2)	2.1 (1.8-2.4)	0.05	2.1 (1.9-2.3)	ns
Ventilation max ($l.min^{-1}$)	69.7 (62.0-77.5)	79.1 (66.3-92.0)	0.01	82.1 (65.8-98.4)	ns
Heart rate max (BPM)	171 (19)	179 (12)	0.04	181 (12)	0.09
Recovery heart rate (BPM)	111 (17)	110 (11)	ns	114 (13)	ns
Test duration(minutes)	9.5 (3.6)	11.4 (3.0)	0.002	11.6 (3.4)	0.002
Total RPE	64 (21)	58 (20)	<0.001	58 (20)	0.04
Submaximum blood lactate ($mmol.l^{-1}$)	2.8 (1.4-3.4)	2.2 (1.5-3.0)	0.09	2.1 (1.4-2.8)	0.04
Peak blood lactate ($mmol.l^{-1}$)	5.8 (2.5)	6.3 (1.8)	0.05	6.4 (1.7)	ns
FVC ($l.min^{-1}$)	3.9 (0.7)	3.1 (0.6)	ns	3.2 (0.5)	ns
FEV1 ($l.min^{-1}$)	3.2 (0.6)	3.8 (0.8)	ns	3.9 (0.7)	ns
FEV1/FVC ratio	83 (5)	81 (6))	ns	83.3 (5.7)	ns
MVC (Newtons)	339 (144)	412 (152)	0.03	381 (88)	0.03

Table 4.13. Physiological variables in flexibility group after 12 weeks of aerobic exercise (cross-over) and at follow up, 3 months after completion. Values are mean (SD) or median (IQR).

Variable	Baseline (n=33)	Post exercise (n=23)	Significance	3 month follow-up (n=20)	Significance vs baseline
V/A total fatigue	324.6 (45.0))	277.0 (60.0)	0.005	250.5 (58.2)	<0.001
V/A physical fatigue	176.5 (16.4))	148.8 (29.1)	0.002	132.8 (33.6)	<0.001
V/A mental fatigue	159 (129-188)	111 (78-144)	0.01	105 (72-122)	0.001
Wessely fatigue	30.5 (5.6)	24.5 (7.4)	0.02	19.4 (9.4)	<0.001
SF36 total score	336 (73)	448 (170)	0.07	479 (153)	0.006
SF36-physical function	46 (18)	62 (19)	0.001	69 (20)	<0.001
SF36-role physical	0 (0-25)	0 (0-75)	ns	38 (0-75)	0.06
SF36-bodily pain	41 (30-52)	56 (28)	ns	64 (23)	ns
SF36-general health	37 (16)	48 (20)	0.05	51 (22)	0.004
SF36-vitality	22 (17-28)	40 (27-52)	0.09	45 (26-64)	0.01
SF36-social function	38 (24)	55 (27)	0.05	65 (27)	0.002
SF36-role emotional	84 (10-117)	100 (75-125)	ns	100 (67-133)	ns
SF36-mental health	64 (60-68)	68 (53-83)	ns	80 (67-93)	0.04
HAD depression	5.0 (2.8)	5.4 (2.9)	ns	5.8 (2.9)	ns
HAD anxiety	4.0 (0.5-7.5)	7.0 (4.8-9.3)	ns	6.5 (4.4-8.6)	ns
PSQI total score	6.5 (3.5)	5.7 (2.8)	ns	5.8 (2.4)	ns
Barsky amplification	10.0 (7.5-12.5)	7.0 (3.3-10.8)	0.006	6.0 (2.1-9.9)	0.05

Table 4.14 Symptomatic variables in flexibility group after 12 weeks of aerobic exercise (cross-over) and at follow-up 3 months after completion. Values are mean (SD) or median (IQR)

Activity Diaries

An analysis of the activity diaries for the two groups is given in table 4.15. The diaries were analysed in blocks of 4 weeks giving a mean duration of activity per week for weeks 1 - 4, 4 - 8 and 8 - 12. The cross-over group spent a similar amount of time involved in aerobic activity as those originally on the exercise treatment, when they crossed over to the graded aerobic exercise programme. In both groups, duration of aerobic activity in minutes per week increased over the 12 weeks of treatment, and significant differences were observed in duration of activity between weeks 1 - 4 and 4 - 8 ($p=0.03$), 4 - 8 and 8 - 12 ($p=0.0009$) and weeks 1 - 4 and 8 - 12 ($p=0.0003$) for the whole group while following the aerobic exercise programme.

Table 4.15. Analysis of activity diaries in minutes of activity per week in giving the mean of each 4 week block. * denotes significant difference with previous 4 week block.

Group	Activity	Weeks 1 -4	Weeks 4 - 8	weeks 8 - 12
Exercise	Aerobic	113 (57)	114 9470*	143 (52)*
Flexibility	Stretching	86 (38)	91 (34))	99 (50)
	Aerobic	99 (46)	104 (49)	143 (80)*

4.2.4 Post exercise pooled data

To further examine the effects of the exercise treatment, the physiological and symptomatic results of all those who had completed the 12 weeks of exercise were pooled at baseline and post treatment. This included the 29 who followed the exercise programme from the start added to those who crossed over to the exercise following the flexibility programme. Those who dropped out during the first 12 weeks and those who did not cross-over were not included in the pooled baseline data. These results are shown in Tables 4.16 and 4.17. Highly significant improvements were observed in the total group in all physiological measures after exercise treatment, except in recovery heart rate and resting lung function, with an 11% increase in absolute VO_2 max, a 20% increase in test duration and a 25% increase in leg strength. Significant positive changes were observed in all symptomatic measures except mental health and bodily pain (SF36), HAD anxiety and depression and the Barsky somatic amplification score, indicating that positive adaptive physiological and symptomatic changes were achieved by all those who had completed the exercise programme.

Table 4.16. Physiological variables at baseline and post exercise (pooled exercise + cross-over group). Values are mean (SD) or median (IQR)

Variable	Baseline (n=51)	Post exercise (n=51)	Significance
VO_2 peak ($ml.kg^{-1}.min^{-1}$)	31.3 (8.1)	33.4 (7.3)	0.004
VO_2 peak ($l.min^{-1}$)	1.9 (1.5-2.3)	2.1 (1.7-2.5)	<0.001
Ventilation max ($l.min^{-1}$)	71.8 (58.7-84.9)	80.7 (63.2-98.1)	<0.001
Heart rate max (BPM)	172 (18)	175 (14)	0.05
Recovery heart rate (BPM)	110 (17)	110 (13)	ns
Test duration(minutes)	10.0 (8.0-12.0)	12.0 (9.8-14.3)	<0.001
Total RPE	67 (54-80)	61 (48-74)	<0.001
Submaximum blood lactate ($mmol.l^{-1}$)	2.9 (1.7-4.2)	2.2 (1.4-3.0)	<0.001
Peak blood lactate ($mmol.l^{-1}$)	5.6 (2.1)	6.3 (2.2)	0.01
FVC ($l.min^{-1}$)	3.9 (0.8)	3.9 (0.8)	ns
FEV1 ($l.min^{-1}$)	3.0 (0.7)	3.1 (0.7)	ns
FEV1/FVC ratio	79 (8)	80 (8)	ns
MVC (Newtons)	309 (226-392)	388 (268-508)	<0.001

Table 4.17. Symptomatic variables at baseline and post exercise (pooled exercise + cross-over group). Values are mean (SD) or median (IQR)

Variable	Baseline (n=51)	Post exercise (n=49)	Significance
V/A total fatigue	320.3 (50.0)	265.4 (54.7)	<0.001
V/A physical fatigue	167.3 (25.6)	138.7 (29.5)	<0.001
V/A mental fatigue	156 (138-175)	120 (100-141)	<0.001
Wessely total fatigue	29.9 (6.6)	22.5 (8.3)	<0.001
SF36 total score	342 (88)	460 (134)	<0.001
SF36-physical function	45 (29-61)	65 (52-72)	<0.001
SF36-role physical	0 (0-25)	25 (0-75)	0.01
SF36-bodily pain	48 (23)	61 (24)	0.08
SF36-general health	38 (15)	50 (18)	0.006
SF36-vitality	27 (15)	41 (17)	0.007
SF36-social function	45 (22-69)	63 (38-88)	<0.001
SF36-role emotional	66 (33-100)	100 (87-117)	0.005
SF36-mental health	65 (15)	68 (20)	ns
HAD depression	5.0 (2.0-8.0)	6.0 (3.5-8.5)	ns
HAD anxiety	6.0 (3.5-8.5)	5.5 (3-8)	ns
PSQI total score	6.8 (3.0)	5.7 (2.8)	0.02
Barsky amplification	9.3 (4.0)	8.3 (4.0)	ns

4.3 Follow up Results

4.3.1 Three months post-treatment

Both treatment (exercise and flexibility) groups were retested physiologically and symptomatically three months after completion of the programme. During this period they did not have regular supervised exercise sessions but advice was given on how to maintain and progress with their exercise sessions and they could remain in contact, mainly by phone. Forty seven of the sixty-six subjects recruited attended for reassessment. Seven had dropped out before the first retest, 7 had not crossed over from flexibility to exercise therapy after the flexibility programme, and 5 could not attend due to leaving the country, change of address or exercise unrelated injury.

The main outcome measure, the CGI score, increased to 69% (18/26) "much better" or "very much better", compared to before the onset of treatment/entry into the study, in those who received only the exercise programme (Table 4.18). 14/21 (67%) of these, who had crossed over to the exercise, rated themselves as "much" or "very much better". This gave a total treatment outcome of 32/47 (68%) who had followed the exercise programme, feeling considerably better three months after treatment, compared to baseline. Figure 4.5 shows the CGI scores following the initial 12 weeks of exercise or flexibility treatment, after cross-over and at 3 months and 1 year follow-up.

Table 4.18. Self-rated CGI change score at 3 month follow-up

Rating score	Exercise (n = 26)(%)	Cross-over (n = 21)(%)
1: very much better	6 (23)	7 (33)
2: much better	12 (46)	7 (33)
3: a little better	6 (23)	5 (24)
4: no change	2 (8)	1 (5)
5: a little worse	0	1 (5)
6: much worse	0	0
7: very much worse	0	0

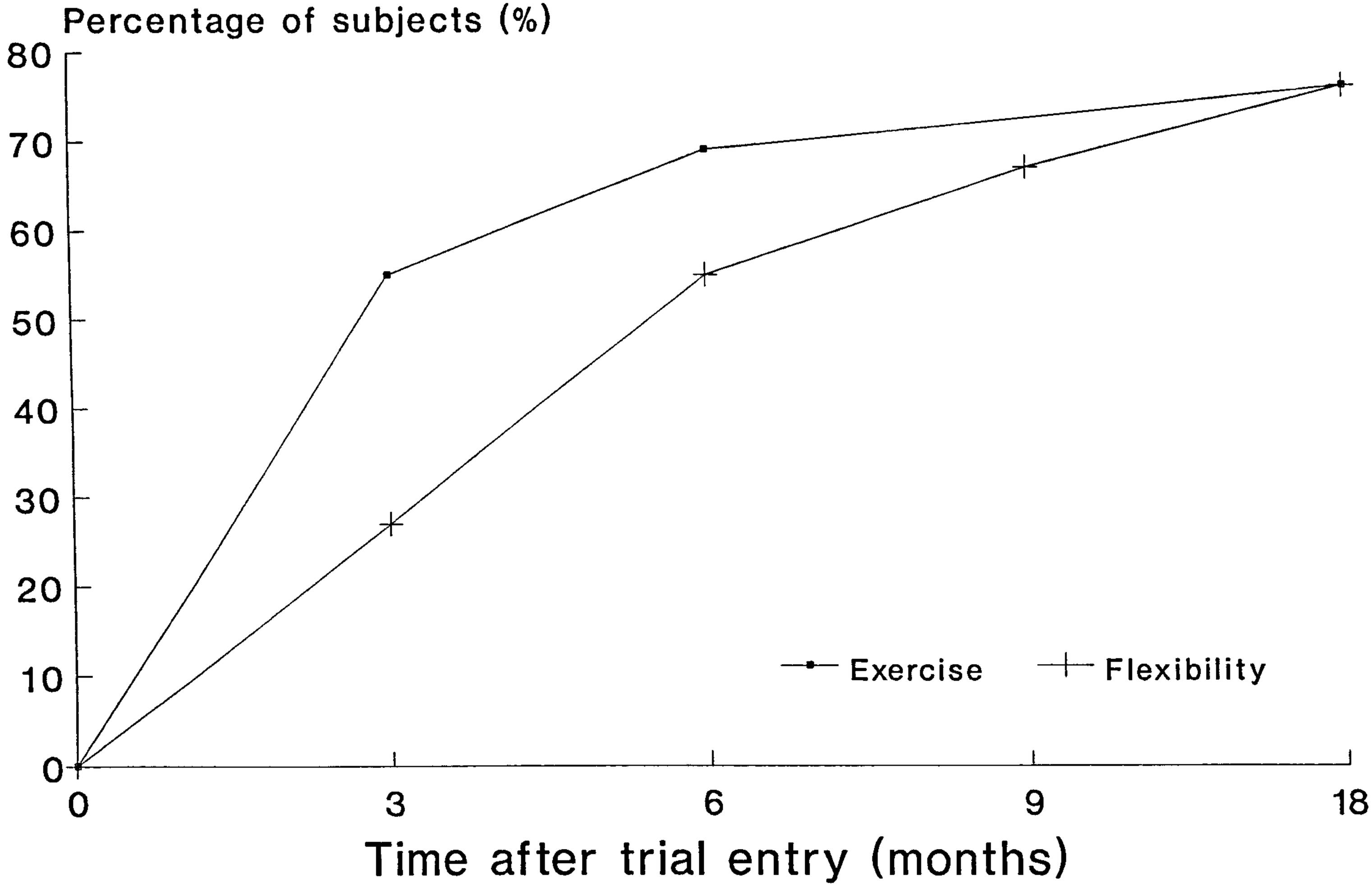

Percentage of Subjects scoring 1 or 2
on the CGI scale
Percentage of subjects (%)
80
70
60
50
40
30
20
10
0
0
3
6
9
18
Time after trial entry (months)
Exercise
Flexibility

Figure 4.5

Physiological results

Compared to baseline, subjects in the exercise only group showed significant improvements in VO_2 peak, both relative and absolute, maximum ventilation, test duration, total RPE score, peak blood lactate and MVC (Table 4.19). Subjects who followed the flexibility programme prior to the exercise programme also improved significantly, in test duration, total RPE score, blood lactate at an RPE of 14 and MVC versus baseline measures (Table 4.13). The increase in peak oxygen uptake and maximum ventilation measured after the exercise programme were not maintained. Significant changes ($p<0.05$) were also observed in submaximal heart rate and RPE at 6, 8 and 10 minutes for both groups at follow-up, compared to baseline, with values of those who had followed the exercise only programme reaching a higher significance level.

Symptomatic results

Compared to baseline self-rated symptomatic measures revealed a significant decrease in fatigue, as measured by the visual analogue scale in total, physical and mental scores and the Wessely total fatigue scores, and improved physical function, social function, emotional role, and total SF36 score in subjects in the exercise only group (Table 4.20). Subjects who followed the flexibility and then exercise programme also showed a decreased total, physical and mental fatigue (visual analogue scale), total fatigue, measured by the Wessely scale, improved physical function, vitality, social function, and mental health, a decrease in the total SF36 score and a decreased score on the Barsky scale (Table 4.14).

Variables	Baseline (n=33)	Post exercise treatment (n=29)	Significance	3 mth follow-up (n=20)	Significance
VO_2 peak ($ml.kg^{-1}.min^{-1}$)	31.8 (7.4)	35.8 (8.1)	0.001	34.0 (8.5)	0.06
VO_2 peak ($l.min^{-1}$)	1.9 (1.4-2.4)	2.2 (1.6-2.8)	<0.001	2.1 (1.5-2.8)	0.005
Ventilation max ($l.min^{-1}$)	71.2 (52-89)	88.6 (67-110)	<0.001	86.7 (62-111)	0.004
Heart rate max (BPM)	170 (18)	174 (17)	<0.001	174 (21)	ns
Recovery heart rate (BPM)	109 (18)	111 (16)	ns	108 (20)	ns
Test duration(minutes)	10.5 (3.7)	12.5 (3.5)	<0.001	12.7 (3.8)	<0.001
Total RPE	73 (21)	68 (18)	<0.001	66 (19)	<0.001
Submaximum blood lactate ($mmol.l^{-1}$)	2.6 (1.4-3.8)	2.0 (1.2-2.8)	0.012	2.5 (2.1-2.9)	ns
Peak blood lactate ($mmol.l^{-1}$)	4.9 (1.9)	6.2 (2.5)	0.09	7.2 (2.3)	0.001
FVC ($l.min^{-1}$)	3.9 (0.8)	4.0 (0.9)	ns	4.1 (0.9)	ns
FEV1 ($l.min^{-1}$)	3.0 (0.7)	3.1 (0.8)	ns	3.3 (0.8)	ns
FEV1/FVC ratio	77 (9)	79 (9)	ns	80.5 (6.5)	ns
MVC (Newtons)	339 (144)	378 (100)	<0.001	481(185)	<0.001

Table 4.19. Physiological variables in exercise group after 12 weeks of graded aerobic exercise and at follow-up 3 months after completion (6 months after baseline measurements). Values are mean (SD) or median (IQR)

Variable	Baseline (n=33)	Post exercise treatment (n=29)	Significance vs baseline	3 mth follow-up (n=27)	Significance vs baseline
V/A Total fatigue	312.1 (49.6))	253.3 (47.6)	<0.001	258.0 (57.0)	0.001
V/A Physical fatigue	161.1 (27.2)	130.0 (27.6)	<0.001	134.0 (32.0)	0.006
V/A Mental fatigue	151 (26.0)	123.7 (30.9)	0.002	124.0 (31.3)	0.001
Wessely total fatigue	28.8 (7.1)	20.5 (8.9)	0.001	21.8 (7.9)	<0.001
SF36 total score	341 (85)	479 (113)	<0.001	448 (97)	<0.001
SF36-physical function	48 (22)	69 (18)	0.002	68 (18)	0.015
SF36-role physical	0 (0-25)	25 (0-50)	0.008	25 (0-50)	0.07
SF36-bodily pain	41 (30-51)	62 (45-79)	0.03	62 (47-77)	0.02
SF36-general health	45 (32-57)	47 (31-63)	0.06	51 (36-66)	0.04
SF36-vitality	37 (25-50)	40 (34-46)	0.04	41 (29-52)	ns
SF36-social function	39 (12-65)	62 (45-79)	ns	63 (51-76)	0.01
SF36-role emotional	52 (61-98)	100 (84-117)	0.009	100 (67-134)	0.01
SF36-mental health	69 (60-78)	76 (65-87)	ns	72 (62-82)	ns
HAD depression	5.0 (1.5-8.5)	5.5 (2.9-8.1)	ns	5.5 (2.5-8.5)	ns
HAD anxiety	5.8 (3.6)	5.5 (2.7)	ns	6.2 (3.5)	ns
PSQI Total Score	6.4 (2.4)	5.0 (3.5-6.5)	0.09	6.0 (3.5-8.5)	ns
Barsky amplification	9.0 (3.9)	8.4 (3.4)	ns	9.1 (4.8)	ns

Table 4.20. Symptomatic variables in Exercise group after 12 weeks of graded aerobic exercise and at follow-up 3 months after completion. Values are mean (SD) or median (IQR).

4.3.2 Three month follow-up: Total post-exercise group (pooled data)

Tables 4.21 and 4.22 show the baseline and follow-up results of only those subjects who had completed the exercise programme (see page 8 for group description). There was a significant difference between groups in relative VO_2 peak at 3 month follow-up, so this data was not included in the analysis. The results of the 47 subjects who completed full physiological and symptomatic reassessment were pooled and analyzed at baseline and compared to their follow-up results 3 months after completion of the exercise programme.

Table 4.21. Physiological variables in exercise and flexibility group (pooled) at baseline and at 3 month follow-up. Values are mean (SD) or median (IQR)

Variable	Baseline	3 month follow up (n=47)	Significance
VO_2 peak ($ml.kg^{-1}.min^{-1}$)	30.9 (8.0)	32.0 (8.6)	0.05
VO_2 peak ($l.min^{-1}$)	1.9 (1.5-2.3)	2.1 (1.7-2.5)	0.003
Ventilation max ($l.min^{-1}$)	71.3 (54.8-87.8)	84.2 (67.8-100.6)	0.002
Heart rate max (BPM)	172 (18)	177 (18)	0.01
Recovery heart rate (BPM)	111 (17)	111 (17)	ns
Test duration (minutes)	10 (8-12)	12.0 (9.6-14.4)	<0.001
Total RPE	67 (54-80)	62 (49-76)	<0.001
Submaximum blood lactate ($mmol.l^{-1}$)	3.0 (1.8-4.3)	2.4 (1.9-3.0)	0.04
Peak blood lactate ($mmol.l^{-1}$)	5.7 (2.1)	6.8 (2.5)	0.002
FVC ($l.min^{-1}$)	3.8 (0.8)	3.9 (0.8)	ns
FEV1 ($l.min^{-1}$)	3.0 (0.7)	3.2 (7.0)	ns
FEV1/FVC ratio	79 (8)	81 (7)	ns
MVC (Newtons)	308 (224-392)	403 (284-522)	<0.001

Compared to baseline significant increases were measured in absolute VO_2 peak, maximum ventilation and heart rate, and blood lactate at an RPE of 14. Subjects continued for a further 2 minutes on the treadmill test giving a significant increase in the test duration, a higher post test peak blood lactate level and a lower RPE throughout the test (and thus a decrease in the

total RPE score). Both heart rate and RPE at 4, 6, 8, 10, 12 and 14 minutes were significantly reduced ($p<0.005$) when compared to baseline (Figure 4.6 & 4.7). In addition oxygen uptake was lower at 4 ($p=0.06$), 6 ($p=0.006$), 8 ($p=0.001$). 10 ($p=0.05$), 12 ($p=0.02$) minutes at follow-up compared to the initial levels (Figure 4.8).

The symptomatic measures revealed highly significant improvements in all measures of fatigue, physical and mental function and general health but not in HAD depression and anxiety scores or the Pittsburgh sleep quality score (as would be expected) or the Barsky amplification score.

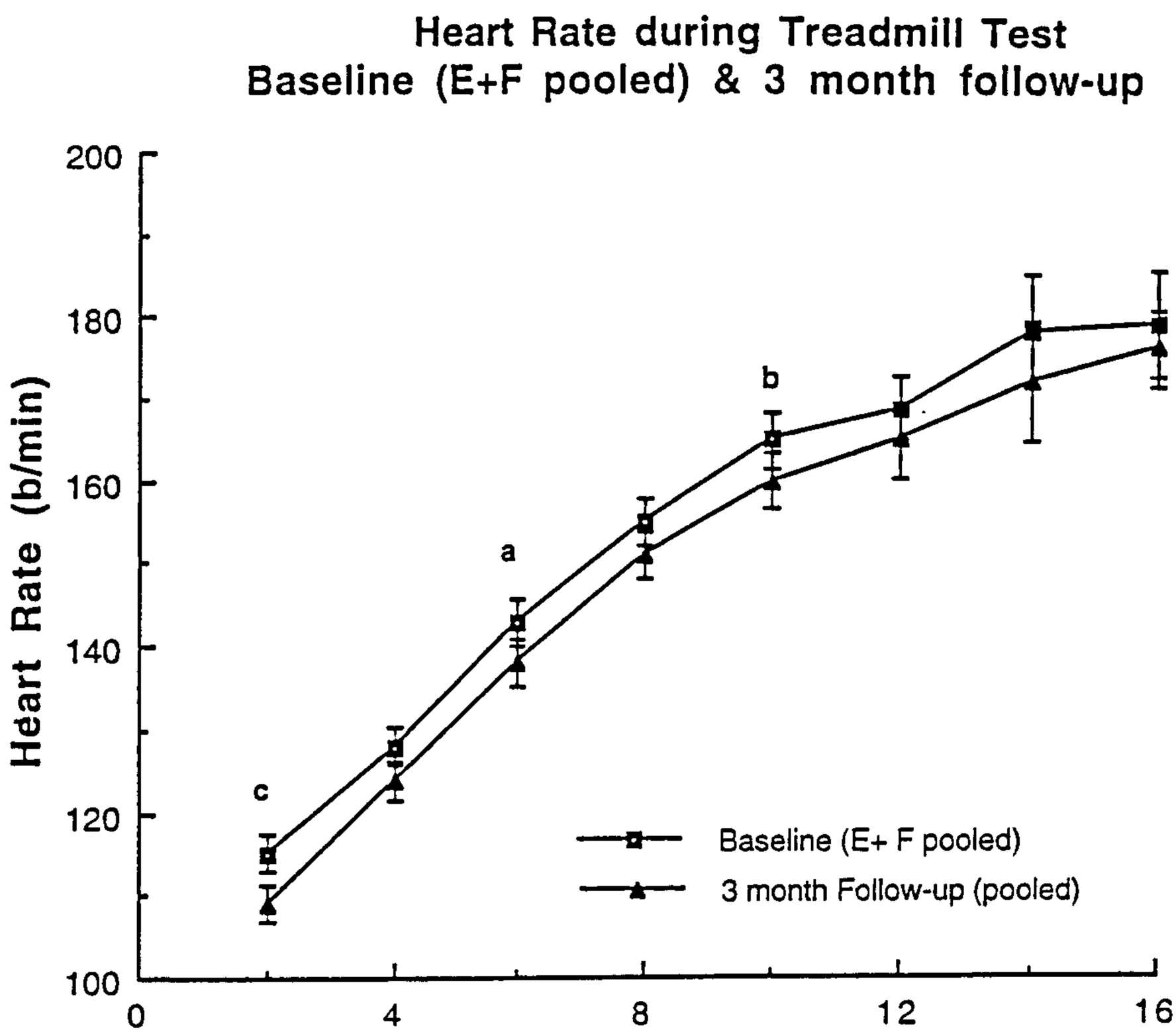
The combined CGI scores for the 47 subjects indicated that 31/42 (68%) considered themselves significantly improved 3 months after following the exercise treatment.

Table 4.22. Symptomatic variables in exercise and flexibility group (pooled) at baseline and at follow up 3 months after completing the exercise programme

Values are mean (SD) or median (IQR)

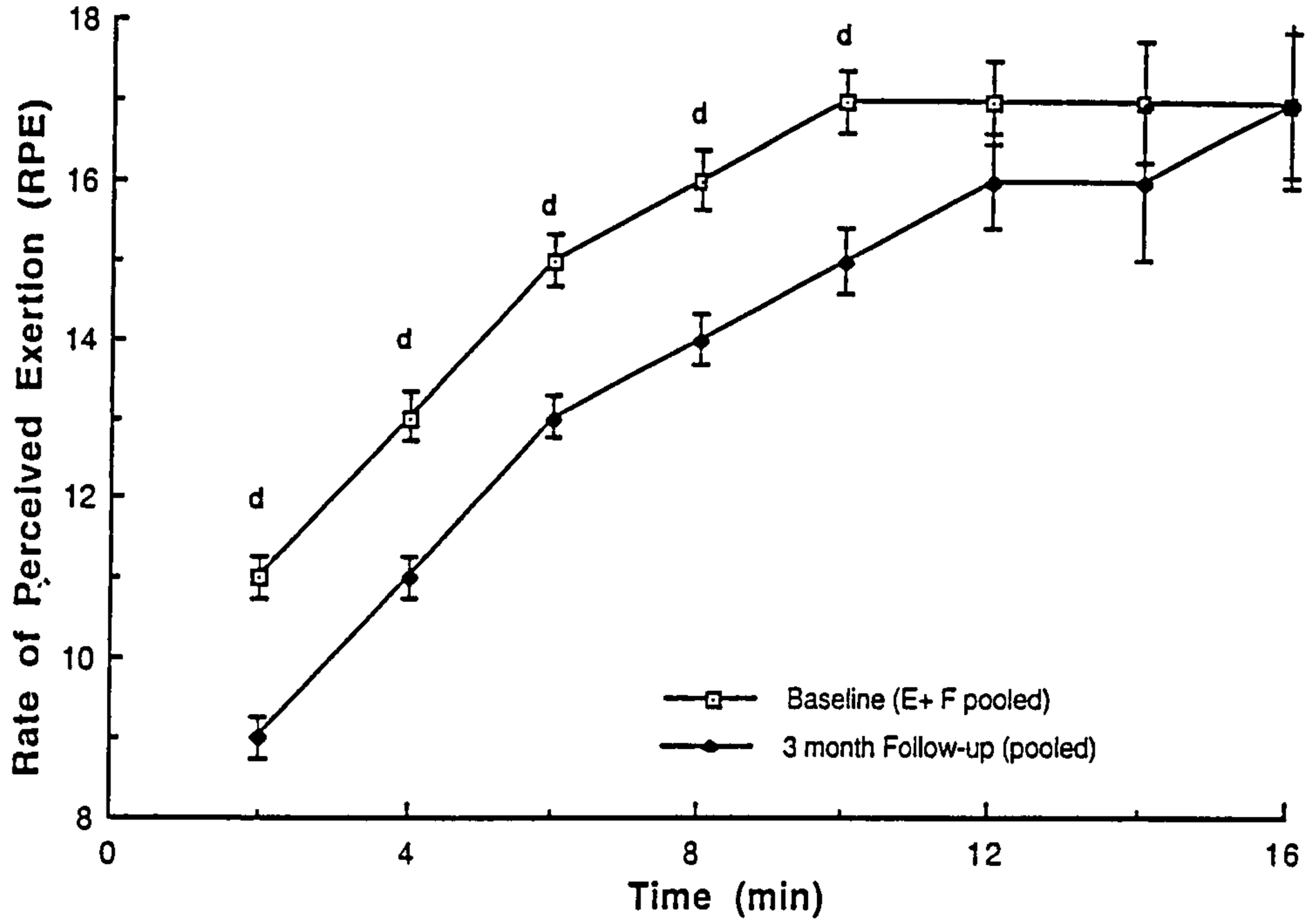
Variable	Baseline (n=47)	3 month follow-up (n=47)	Significance
V/A total fatigue	319.8 (47.4)	254.7 (57)	<0.001
V/A physical fatigue	166.8 (23.1)	133.5 (32.4)	<0.001
V/A mental fatigue	158 (140-176)	110 (88-132)	<0.001
Wessely total fatigue	29.9 (6.5)	20.8 (8.5)	<0.001
SF36 total score	340 (84)	442 (125)	<0.001
SF36-physical function	45 (31-59)	70 (57-83)	<0.001
SF36-role physical	0 (0-25)	25 (0-50)	0.01
SF36-bodily pain	47 (23)	62 (42-82)	0.003
SF36-general health	39 (15)	51 (20)	<0.001
SF36-vitality	26 (15)	43 (21)	0.001
SF36-social function	44 (19-69)	63 (51-76)	<0.001
SF36-role emotional	52 (14-89)	100 (67-134)	0.005
SF36-mental health	64 (15)	73 (19)	0.01
HAD depression	5.0 (1.6-8.4)	6.0 (3-9)	ns
HAD anxiety	6.0 (3.5-8.5)	6.0 (4-8)	ns
PSQI total score	6.8 (2.6)	6.1 (3.1)	ns
Barsky amplification	9.1 (4.0)	8.6 (5.2)	0.08

Figure 4.6



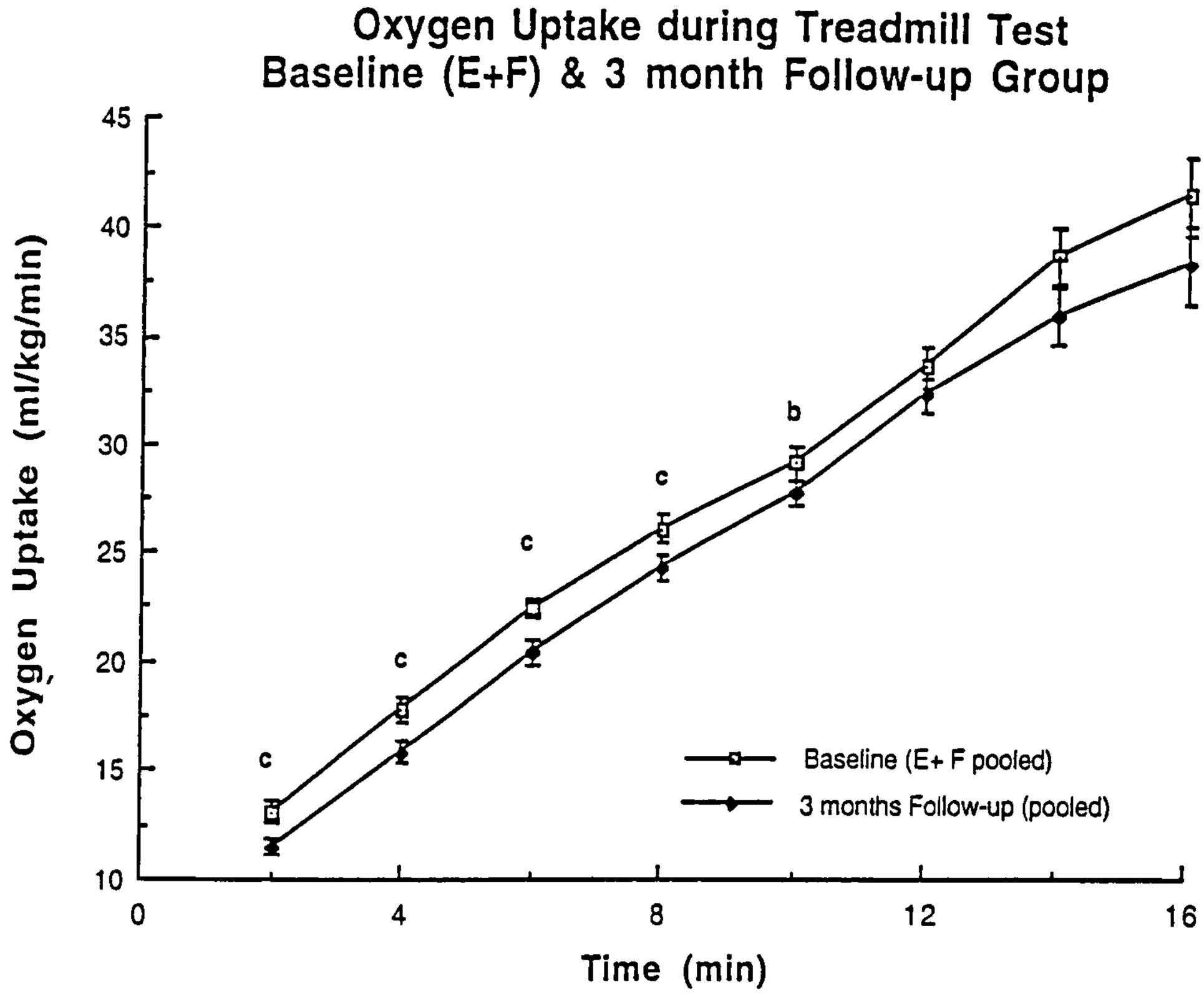
Statistically significant differences denoted as follows ~
a, P< 0.05; **b**, P< 0.02; **c**, P,< 0.01; **d**, P< 0.001

Figure 4.7



Statistically significant differences denoted as follows ~
a, P< 0.05; **b**, P< 0.02; **c**, P,< 0.01; **d**, P< 0.001

Figure 4.8



Statistically significant differences denoted as follows~
a, P< 0.05; **b**, P< 0.02; **c**, P,< 0.01; **d**, P< 0.001

4.3.3 One year follow up

Forty-seven of the 66 patients replied to the follow-up questionnaires approximately one year after treatment was completed. On the CGI score, 76% (32/42) of those who had followed the exercise programme rated themselves "much" or "very much better" compared to baseline, on entry into the study. Of the 10 who had flexibility treatment alone, 5 replied, 2 of whom were significantly better, 1 of whom had done her own exercise programme.

There was a significant difference ($p=0.05$) in the number of subjects who were working or studying when compared to baseline, with 66% (31/47) working at 1 year versus 38% (25/66) at baseline, combining the figures of those working full- and part-time. When broken into respective part- or full-time work/study hours, 40% (19/47) were working full-time at 1 year follow-up compared to 20% (13/66) at baseline, and 26% (12/47) were working part-time at follow-up compared to 18% (12/66) at baseline, with 62% (41/66) not working or studying at all. Premorbid employment details revealed that 88% (58/66) were working full-time, 4.5% (3/66) part-time and 7.5% (5/66) were not working before their illness at all.

Sixty-eight percent (32/47) had continued with exercise and considered themselves regularly active, which is higher than the proportion of subjects who regarded themselves as regularly active before they ever fell ill (55%)(36/65), but not significantly so. In addition, the visual analogue scores for physical ($p<0.0001$), mental ($p=0.0003$), and total fatigue ($p<0.0001$) all increased significantly compared to baseline. We also analysed separately the visual analogue scores of those who rated themselves a CGI score of 1 or 2 (i.e. recovered/much better) to determine if their fatigue rating had returned to normal levels. This gave scores of 119 (35), 114 (37) and 233 (64) for physical, mental and total fatigue, respectively. A score of 100 on physical and mental and 200 on total fatigue would indicate no fatigue. There was a significant difference ($p<0.001$) in total fatigue on this scale between baseline (316(48)) and follow-up (230 (63)) for all those who had completed the exercise programme.

4.4 General Discussion

A significantly greater proportion of subjects (55 %) rated themselves as "very much better" or "much better" after graded aerobic exercise treatment, compared to flexibility and relaxation alone (27 %). This was an effect size of approximately 100 per cent compared to an active intervention, i.e. 100% more were better with the exercise treatment than the flexibility treatment (difference in % of the treatment group getting better divided by the % of placebo getting better). Only one subject in each group felt worse after completing treatment and both of these had developed a major depressive illness, with the treatment itself not responsible. The development of the depressive illness in both cases was consequent on life events and not attributed, by the subject, to the treatment. Analysis by intention to treat gave similar results, with low drop-out rates. Exactly the same percentage of cross-over subjects rated themselves as better after three months of exercise, giving further support to the original exercise group results. This also suggests that there is no advantage in beginning with flexibility alone and introducing patients to regular activity through a more gradual approach, since three months of exercise treatment was as effective as six months of a more staged approach of flexibility followed by aerobic exercise. Starting with a 3 month flexibility programme might alleviate any worries that an aerobic exercise programme might be too strenuous, but this approach offered no advantage to the final outcome. This outcome was maintained or exceeded at follow-up 3 months post-exercise treatment, by both patient groups, regardless of initial treatment, giving a total group outcome, 3 months after completion of the exercise programme, of 68% improved. At one year follow-up, three quarters were better, with an accompanying return to pre-morbid levels of physical activity, but incomplete return to work.

The subsidiary outcome measures of fatigue and functional capacity confirmed the superior improvement with aerobic exercise. The lack of change in measures of mood, mental fatigue and mental health suggests that successful treatment was independent of antidepressant or anxiolytic effects. Although a minority of subjects were taking antidepressant medication, this was maintained the same throughout the study with no differences between the two treatment

groups. Therefore, antidepressants cannot have been responsible for the differences between treatments.

The drop out rate of 11% is comparable to other exercise studies with similar patient groups. A study using exercise with chronic low back pain sufferers (Frost et al, 1995) had a 12% drop-out, similarly 12% patients dropped out of an aerobic exercise study with patients with chronic respiratory disorders (Goldstein, 1993). Veale et al (1992) had a 25% drop-out rate from their exercise programme with depressed patients, which involved a programme of 3 supervised sessions per week. Interestingly, a recent combined exercise and drug treatment trial with CFS patients, which included those with psychiatric disorders, had a much higher drop out rate of 29% (Morriss et al, 1996). This may highlight the importance of excluding patients with major psychiatric disorders which could affect their participation in and adherence to a treatment programme, as well as allowing us to examine the effects of the treatment on pure fatigue syndrome, rather than a fatigue syndrome confounded by other potential disorders.

Regular and progressive aerobic activity produced measurable and significant increases in aerobic capacity, as measured by a 13 per cent increase in peak VO_2, an increased maximum ventilation and treadmill test duration. These changes in peak aerobic capacity are consistent with previous results with a group of healthy sedentary individuals performing low intensity training (50% VO_2 max) for 30 minutes, three times per week, in which maximum aerobic capacity was increased by 5 - 10% after 6 - 12 weeks (Blomqvist & Saltin, 1983). Similarly, Jette et al (1988), measured a 12 per cent increase in relative VO_2 max in a group of sedentary middle-aged males and females who exercised for 30 minutes, 3 times per week at 60% VO_2 max for twelve weeks. An even larger increase (27%) was measured by Steinhaus et al (1990) with a group of 55-70 year old subjects after 4 months of walking or jogging at 60-65% of their VO_2 max initially, increasing to 70-85% max heart rate . The 13% increase observed following exercise in the current study indicates that it is possible to find measurable increases with a very low intensity exercise programme in a previously inactive group. The main reason for highlighting these studies is to point out that very sedentary, unfit or elderly individuals, which would also encompass the typical CFS patient, in terms of

baseline physiological capacity, can experience the same magnitude of improvement, in terms of a training response, as a more able, fit or healthy individual. This applies even when the exercise programme followed is relatively mild in intensity and duration, and quite possibly below the threshold intensity that one might consider necessary to stimulate a training effect.

A clear link has been established between the enhancement of an individuals aerobic capacity and their ability to cope with the demands of their lifestyle (Bird, 1993). The positive effect of the exercise programme on functional capacity was confirmed by the significant inter-group differences in both physiological and functional capacity after three months of treatment. This is a relatively short space of time to see measurable training effects, particularly considering that the duration of illness ranged from a minimum of 9 months up to a maximum of 19 years. However, when working with deconditioned or very sedentary groups of individuals, relatively small changes in biological variables can produce substantial improvements in functional capacity and thus a positive clinical outcome. Frequently, those individuals who start with a relatively low level of fitness improve the most, when expressed as a percentage of maximum oxygen uptake and it may be that only a small amount of exercise is sufficient to promote positive adaptations. Haskell (1994) and Astrand (1970) suggested that more benefit is achieved when the least active persons take up exercise, than when more active individuals increase their activity by a similar amount, and he put forward a model, showing that, for any given amount of activity, the magnitude of benefit is inversely associated with the baseline activity level. The previous results (4.1) confirmed that the groups in the study were considered both low-active and unfit compared to normal healthy, but sedentary individuals, and therefore, were likely to respond well, with regard to improvements in physiological capacity, even with a very moderate amount of activity. Indeed some of the CFS patients had spent extended periods in bed or had adapted their lifestyles to get through essential daily tasks interspersed with periods of rest or sleep. Undoubtedly this would have a detrimental effect on their physiological capacity, to the extent that that the addition of even a small amount of physical activity was sufficient to initiate a training or exercise effect - physiological or psychological.

The chosen low intensity of exercise, particularly at the early stages of the training, and indeed the total volume of exercise, may be considered too low for noticeable improvements in fitness, as it is considerably below the original American College of Sports Medicine (ACSM) recommendations for the amount of exercise necessary for "developing and maintaining fitness in healthy adults". (ACSM, 1978). Indeed, the landmark paper by Karvonen (1957) suggested that training had to increase the heart rate to above 140 beats per minute to cause an increase in VO_2 max. However, since then, several researchers have tried to determine the minimal threshold or intensity of exercise necessary to improve either fitness, health or both. Haskell (1992) compared responses to 15 weeks of aerobic activity at 85% or 45% of maximum aerobic capacity and found that over the shorter term greater changes were seen in the 85% group but over the longer term, a 9% increase was also seen in the group exercising at 45%, with a greater adherence and fewer drop-outs in this group. Similarly, a 20 per cent increase in VO_2 max was measured after a 12 week aerobic exercise programme at 60% VO_2 max in a group of previously sedentary middle-aged women (Johannessen et al, 1986).

Lower intensity exercise may encourage greater adherence to exercise programmes, particularly for previously sedentary or deconditioned individuals. A study comparing 10 weeks of high intensity to moderate-intensity aerobic training, attention-placebo control and waiting-list control found that only the moderate-intensity exercise group demonstrated benefits in variables associated with well-being, in older, sedentary individuals (Moses, 1989). It appears that moderate intensity activity performed by previously sedentary middle-aged and older men and women results in significant improvements not only in aerobic capacity but in other health measures, and, for enhancing health, it may be more important to promote an increase in the volume, rather than intensity, of activity. This lends support for the value of low to moderate intensity activity for the chronically sedentary, overweight individuals, patients and the elderly. Low intensity "non-demanding" exercise can also lead to greater psychological benefits and increased compliance. Sexton et al (1989) recommended that therapeutic exercise should consist of regular, light. self-selected exercise, for 30

minutes, several times per week, which is adequate for beneficial effects, whilst minimising drop-out. The low intensity of exercise used with the CFS patients in this study was not only sufficient to allow adaptive physiological effects, but was also manageable enough to promote good adherence, since patients felt able to cope with the demands of the exercise and were less inclined to drop out. Those who did drop out in this study did not do so because of the demands of the exercise programme, but for more domestic reasons.

The peak VO_2 of 30.6 $ml.kg^{-1}.min^{-1}$ for the CFS group as a whole (n=66) at baseline was just below the average level expected for healthy individuals (36 - 40 $ml.kg^{-1}.min^{-1}$) in the 30 - 39 year age range (McArdle et al, 1994). This was reached at 91 (8) and 92 (9)% of their age predicted maximum heart rate in the exercise and flexibility groups, respectively, indicating that the subjects were motivated to continue the test to perceived physiological maximum. The issue of whether we can presume that the CFS patients actually pushed themselves to maximum has been discussed previously in section 4.1.3. Previous studies have suggested that reduced motivation or increased pain are both common problems when testing CFS patients, as they report higher perceived effort and pain at any given workload than healthy individuals (Riley et al, 1990; Gibson et al 1993). However, it would be expected that any new activity would feel more strenuous and/or painful, particularly if associated with a greater lactate production, for an individual who has taken part in little or no activity for an extended period. The result of this would expectedly be an increased perceived exertion rating on the RPE scale, which may be considered inconsistent with the level or intensity of exercise they are doing. Following the exercise programme, the mean VO_2 peak for the exercise group increased to 34.8 $ml.kg^{-1}.min^{-1}$ which was closer to the optimum range for healthy individuals. When the male and female data was analysed separately, it was found that the males were just within the normal range before treatment, whereas the females were below this normal range. Following the exercise treatment, mean values for the men exceeded the optimum range whereas the females reached the lower end of this range. Some of the male subjects in the study had previously been very active participants in sport prior to their illness, such that one would speculate that their premorbid VO_2 peak would have been well above the optimum range for the general population. Some men were beginning to

incorporate jogging into their exercise programme towards the end of treatment, again accounting for the greater increase in peak VO_2 values in males. The significant increase in maximum ventilation is consistent with an increased aerobic capacity and is most likely to be due to the subjects utilising a greater proportion of their available lung volume after training. Badenhop et al (1983) measured increases in maximum ventilation of 10 litres (25%), on a low intensity training programme at 30-45% VO_2 max, performed 3 times per week with a group of elderly deconditioned subjects, which is similar to the 24 per cent increase in maximum ventilation measured in the exercise group in the current study. Improvements in peak aerobic capacity serve to indicate that it is possible for a group of individuals with very low levels of aerobic fitness to follow a programme of regular exercise at a very low intensity and to see measurable improvements. In a relatively short space of time, they can reach levels expected for healthy individuals in the general population, i.e. levels consistent with a normally active lifestyle. However, this is not to say that VO_2 max is the most important determinant of lifestyle activity, but it remains a good starting point from which to assess a person's capability.

The differences between the two groups in the blood lactate response to exercise was not significant when re-tested after 12-weeks, but the mean percent change in the exercise group (30%) was significantly higher, whereby the blood lactate concentration at the same test stage decreased from 2.6 to 2.0 $mmol.l^{-1}$ after training, with no change in the flexibility group. This indicates a lower blood lactate production for the same exercise intensity after the 12 weeks of exercise, i.e. a greater metabolic efficiency and a switch to a greater reliance on aerobic metabolism. In realistic terms for the CFS patients, this lowered lactate level during exercise would allow them do more or continue for longer in any activity without the discomfort or pain associated with lactate accumulation in and around the working muscles. One of the documented short-term effects of regular exercise is an increase in the capacities of the major metabolic pathways to release energy, which ultimately reduces local fatigue and discomfort in the exercising muscles, because less lactic acid is produced (Astrand & Rodahl, 1986).

In line with the increased test duration in both groups, there was an increased post-test peak blood lactate concentration, potentially indicating an increased ability to tolerate the lactate produced as a result of the exercise and implying a higher pain threshold following either programme. This may be partly as a result of participation in the programme, which allows them to put into a better perspective, the discomfort that can be associated with new or increased exercise participation, particularly after a long period of inactivity. When they began, this pain or signal to stop the test was probably partly due to fear of activity *per se* and of causing a relapse or of overdoing it, as well as a lack of familiarity with the sensations of strenuous levels of exercise. After following an exercise programme, gaining a better understanding of exercise and, probably, experiencing a certain amount of pain or discomfort in the process, they felt more confident in their ability and more prepared to push themselves further. A similar study design (aerobic vs flexibility training) with sedentary, elderly individuals, measured an increased aerobic capacity in their flexibility treatment group (Steinhaus et al, 1990). The authors suggested that the upper heart rate limit of 100 BPM for the flexibility training group was sufficient to allow cardiorespiratory training to occur in a group who had previously been very inactive. Since the flexibility group did not wear pulse monitors while stretching, we cannot determine whether the heart rate was sufficiently elevated to allow some aerobic training effects. Badenhop et al (1983) had previously demonstrated that elderly and sedentary individuals can significantly improve their aerobic capacity at heart rates of 30 - 40% of maximum. In addition, many subjects in the current study noted a reduction in anxiety about tackling physical tasks, during the programme, which encouraged them to be more active in their normal daily lifestyle, and those in the flexibility group (as well as the exercise group) reported becoming more active generally, as they relaxed and undertook a planned programme. This general increase in activity, although not formal exercise, may also have been sufficient to increase certain parameters, particularly in the flexibility group, who also showed a greater exercise tolerance after the 3 months. However, an increased maximum aerobic capacity was only measured in those subjects who had followed the exercise programme, and those who initially followed the flexibility programme did not show a significantly increased aerobic capacity until they had crossed

over into the exercise treatment. Related to this, self rated symptomatic improvement in physical fatigue, physical function and general health were greater following the more strenuous exercise programme. It could be argued that the physiological improvements measured after the flexibility treatment were sufficient, and that they were achieved with a much less strenuous and demanding treatment than the aerobic exercise programme. However, irrespective of this, the patients themselves did not rate their improvement as significant after the flexibility programme, with only 27% feeling much better compared to double this percentage after the exercise treatment. Taking this into account, and also considering the significant differences in the symptomatic measures of physical function, fatigue and general health, it appears that the CFS patients do not actually feel or notice such a large improvement in symptoms until they experience noticeable physiological changes. Alternatively, it could be that taking part in a more strenuous programme of aerobic exercise, is a greater stimulus to make them feel that they are taking control of their illness and actively reversing the deconditioning. The increase in metabolic rate, body temperature and heart rate associated with aerobic activity is far more exhilarating than would be experienced after stretching, such that even if they are only doing a relatively small amount of aerobic exercise, they may still feel that they are taking a more positive approach to treatment. This is possibly what is reflected in their CGI scores and the symptomatic measures.

In determining whether a group of CFS patients have reduced exercise tolerance or strength, the result frequently depends on the comparison group used, the test mode, or the end point criteria. However, the results of the current study show that this initial baseline level, determined by the subjects' own perception of maximum, can be significantly increased. There was a definite trend ($p=0.08$) towards an increased test duration following the exercise programme, compared to the flexibility treatment. As would be expected, more marked improvements in exercise response were observed at submaximal levels of exercise in both heart rate and RPE at 6, 8, 10 and 12 minutes of treadmill walking, where significant decreases were measured at all stages for both parameters, following the exercise programme. There were more noticeable changes in physiological parameters at the intensities at which patients had been exercising (40 - 60% of their maximum capacity)

rather than at maximum levels, due to an improved efficiency and economy of effort leading to a reduced perception of effort at these intensities. This was further confirmed by the significant difference between treatments in area under the curve for submaximal heart rate between groups after 12 weeks of treatment ($p=0.02$) and perceived exertion rating ($p=0.04$) (Figures 4.3 and 4.4). This effect was also reported by Newham and Edwards (1979) after just 2 weeks of cycling two to four times per week for up to 30 minutes, with a reduced exercise heart rate at 85 watts, in a group of patients with "effort syndrome".

A high heart rate tends to lower the mechanical efficiency of the heart which may, with a lowering of the stroke volume which can, in turn, reduce the amount of oxygen delivered to the muscles. We would expect changes to be more significant at the intensities at which the individuals had exercised rather than at maximal levels, which were never reached during the exercise programme itself. One of the more significant adaptations to training is a slowing of the heart rate at any given exercise intensity, thus reducing general physiological disturbance and significantly lowering the intensity of sympatho-adrenal activity (McArdle et al, 1986). The slower heart rate reduces myocardial work, which is important since heart rate is the major determinant of energy expenditure by the heart muscle. Greater submaximal improvements were also observed by Cramer et al (1991), in a group of sedentary women walking 5 times per week, at 60% of maximum heart rate for 15 weeks. They measured a significant improvement in submaximal heart rate and ventilation but no increase in maximum oxygen uptake or ventilation. However, highly significant improvements were measured in general well-being, particularly "energy level" and "freedom from health concerns and worry" which were strongly correlated with improvements in submaximal fitness for all subjects.

As described earlier, the highest level reached in the isometric strength test was recorded, as well as whether this was achieved with or without electrical stimulation. The twitch interpolation technique was used to assess whether they could fully activate the quadriceps muscles but, due to limitations in equipment, the difference between voluntary maximum and

that added by the twitch could not be measured accurately. Therefore, when discussing MVC, it implies the highest level recorded from the 5 trials on each assessment.

In contrast to previous studies which found no significant difference in strength in CFS patients compared to healthy controls (Stokes et al, 1988; Rutherford and White, 1991), the highest levels recorded in the MVC test, with or without stimulation, were lower than the controls. Both groups significantly increased their quadriceps strength level from baseline with treatment. Values for the maximum isometric strength test can be compared with normal ranges for height and body mass (Edwards et al, 1977). The mean pre-treatment value for both groups of patients of 339 Newtons was below the expected range of 375 - 650 Newtons, but following the graded aerobic exercise programme, the mean value was increased to within this range (430N), and just reached the lower end of the range following the flexibility programme (378N). No specific strength training was done as part of either exercise regime. Therefore, any strength improvements were more likely to be due to a generally more active lifestyle, and in the case of the flexibility group, possibly a reduced muscle tension resulting from the stretching programme. Pain and stiffness are often felt in muscles and joints during and after flu-like illness, which is not dissimilar to some of the symptoms described by CFS patients, and this may also inhibit muscle contraction, such that improved flexibility can influence this. Those patients who began in the flexibility group and then continued with 12 weeks of graded aerobic exercise showed further increases in MVC from 378 (182) to 412 (152) Newtons putting them within the expected range for their weight.

An independent lifestyle may become impossible when major muscle groups, such as the quadriceps, become weak, with important implications for both health and lifestyle. Taking the optimum range for MVC (50-75% body weight) recommended by Edwards et al (1977) into account, the lower limit for the current group should be approximately 340N with an optimum of 500-520N (75%). Therefore, improvements enabled CFS patients to increase their strength levels from the lowest level, up to 62% and 56% of body weight after the exercise and flexibility programmes, respectively, with no specific strength training involved.

The cross-over group increased to 62% of body weight following the exercise programme. Considering the low initial levels measured, it would be recommended that future exercise programmes with CFS patients should incorporate strengthening exercises for the legs and also the upper body. This would also take into account the recommendations by Edwards et al (1977) for minimum strength levels in the major muscle groups, such that they could expect to reach the levels consistent with a independent lifestyle.

The measures of body fat, body mass index and resting lung function were taken for the point of determining if patients were within normal or expected ranges. There were no significant changes in body fat levels or body mass index during the course of the programme, with both flexibility and exercise treatments. This would be as expected with the levels of exercise that the patients were doing. Although individual patients may have experienced small decreases in body fat (total skinfold) levels, the difference was small and non-significant for the whole group. This measure would have had little effect on the treatment outcomes, but it was important to establish that there were no significant differences in body composition between groups prior to treatment. For this reason, and the lack of change in these measures, the post-treatment values were not reported. Since resting lung function was within desired ranges, indicating that there were no observed airways obstructions or restrictions that might limit exercise response, it is again not unusual that there were no significant changes in these measures over the course of the treatment.

Some research has examined the beneficial effects of exercise on several other chronic conditions whereby patients have traditionally been recommended to restrict their activity (Kottke, 1984; Basmajian & Wolf, 1990). A few studies have measured large increases in cardiovascular fitness in fibromyalgia patients following a programme of regular aerobic exercise compared with a flexibility programme (McCain et al, 1988) or no treatment (Mengshoel, 1992). McCain et al (1988) found that 50% of fibromyalgia patients showed a clinical improvement with 3 x 20 minute exercise sessions per week for 20 weeks, compared to a 10% improvement with flexibility. The improvements related to the exercise programme were unrelated to changes in psychological stress levels, suggesting that the positive effects of

exercise were not mediated through a reduction in stress levels. However, both of these studies used fully supervised exercise sessions throughout, whereas the current study involved only one supervised exercise session per week, with prescribed sessions for the remainder. In ore for the long term, this gives the responsibility and control to the patient, with the aim of developing a self-regulated exercise habit suited to the individual's lifestyle, but this may not produce such dramatic results in the short-term.

Goldstein et al (1994) studied the use of exercise in the rehabilitation of patients with chronic obstructive pulmonary disease (COPD), a group of patients who would also be expected to be deconditioned. This also involved supervised exercise sessions for the first 8 weeks, followed by 16 weeks of unsupervised activity. The exercise programmes used an interval approach, interspersing low and moderate intensity activity, to attain a sufficient duration of activity, combining treadmill walking, upper body ergometry and mobility exercises. Significant inter-group differences were found on re-testing in physiological measures of walk distance and submaximal cycle time and on self-rated measures of dyspnoea, fatigue, emotional function and mastery. The authors suggested that the self-rated questionnaire replies may be a better reflection of function than measurements of walking or cycling, particularly since they quote a study by Toshima et al (1990) with a similar group of patients, in which they measured a 57% improvement in treadmill time, but no improvement in quality of life. This would lead us to question which are the more important improvements, and helps to emphasise the importance of the patient-rating on the CGI score as the main outcome measure in the current study, above and beyond the physiological improvements, since it is the patients' own perception of illness or recovery that will have the most influence on their ability to resume and maintain normal daily activities.

By way of comparison, Nordemar et al (1976) carried out a 16-week physical training programme with 10 rheumatoid arthritis patients, involving 2 hours of supervised activity per day (3-4 minutes cycling at 50-70% VO_2 max interspersed with 2 - 5 minutes rest, quadriceps strength training, walking and stair-climbing), on 5 days per week. Four out of 10 patients had a decrease in tender joints. Mean improvement was 6% in walk test duration, 11% on the

stair test, 25% increase in bicep strength and a 35% increase in maximal physical work capacity. They also found significantly improved psychological status. The *prescribed* exercise in the current study was considerably less intensive, but still resulted with a 27% increase in isometric quadriceps strength, a 19% increase in walk test duration and a smaller, 13%, increase in maximum aerobic capacity (the pooled exercise data resulted in 20%, 14% and 10% increases in strength, test duration and VO_2 max, respectively). In contrast to Nordemar's results, a relatively modest increase in aerobic capacity, in this study, translated to a large increase in test duration and thus exercise tolerance, and a similar magnitude of increase in strength of a larger and perhaps more important muscle group, without any specific strength training. As mentioned previously, patients involved in an exercise programme tend to become more active throughout the day, as confidence increases and they take on previously avoided tasks, which may explain the large increase in strength despite the absence of a prescribed strength training programme. Weyerer and Kupfer (1994) have also suggested that just participation in a regular exercise programme *per se* may produce a sense of accomplishment and enhanced self-sufficiency.

The studies just discussed serve to highlight the fact that the use of graded exercise therapy in many different forms and structures has been used successfully with several different chronic illnesses in the past. This approach would not have been the most conventional treatment for conditions such as rheumatoid arthritis or COPD but was associated with significant improvements in patients' well-being and symptoms. Based on these results it is equally appropriate to explore and examine the use of exercise with CFS as in this study, and to incorporate some of the positive aspects of previous work. A recent study with a similar design to this one compared a 4 week aerobic and circuit type exercise programme with standard medical care (lifting techniques and posture control) in a group of 81 patients with chronic low back pain (Frost et al, 1995). Significantly greater improvements were reported on the main outcome measure - the Oswestry low back pain disability index - after the exercise programme compared to the control treatment, and this was maintained at 6 months. Improvements were also observed in self-efficacy, willingness to tackle physical tasks and in walking capacity, but not in general health. Twelve patients from the control group, who

crossed over to the exercise treatment after the second assessment, reported less disability, but these differences were not significant. This is similar to results of the cross-over group in the current study who showed less physiological improvements than the original exercise treatment group, although symptomatic improvements were observed. It appears that smaller physical changes are seen when patients are given an alternative therapy prior to the main treatment and this may be important in determining the patient's attitude to particular treatments. This may have influenced the attitude of the original flexibility group towards exercise throughout their involvement, whereby they regarded flexibility exercise to be equally as important as aerobic activities in their treatment. This will be discussed further later.

On the symptomatic measurements, random allocation into groups, did not prevent baseline intergroup differences in physical fatigue as measured by the visual/analogue (V/A) scale and in SF36 vitality. Therefore, percentage changes versus baseline in measures were calculated after the 12 weeks on either treatment, resulting in significantly greater positive changes in fatigue following the exercise treatment compared to flexibility, and physical fatigue at baseline did not have any effect on response to treatment (ANCOVA results). This was further indicated by the highly significant intergroup differences in these measures after treatment. Further significant positive effects were measured in V/A total fatigue, Chalder fatigue, which incorporates both physical and mental aspects of fatigue, SF36 total score and physical function, with a tendency towards improved physical role following exercise treatment. These improved SF36 scores indicate that subjects after the exercise programme perceived less problems with work or other daily activities and that they felt that they could undertake physical activities without limitations due to health. This complies with a greater tendency to tackle physical tasks during their normal daily lifestyles, that they had previously felt were restricted by CFS effects. One of the theories about the effects of exercise on a person's psychological health suggests that exercise can lead to a feeling of mastery or a way of regaining control over their bodies which can, in turn, lead to increased confidence and self-efficacy, which may generalise to other areas of their life (de Coverley Veale, 1987). Several mechanisms have been proposed for the psychological effects associated within

regular exercise. Those most relevant to CFS patients, include improved physical fitness, providing people with a sense of mastery, self-control and self-sufficiency. Exercise provides a distraction, diversion or time-out from unpleasant cognitions, emotions and behaviour. Alternatively, exercise competes with negative affects, such as anxiety and depression, in the somatic and cognitive systems (Weyerer & Kupfer, 1994). In this respect, patients learn to overcome a major barrier that may have prevented them from leading a normally active lifestyle. This barrier could be both mental and physical leading to a two-pronged effect of the exercise programme.

No changes were observed in HAD scores with treatment in either group, but this is to be expected since the mean scores for both anxiety and depression were below case level at baseline (below 7) (Zigmond and Snaith, 1983). The authors give a score of 8 - 10 for borderline and above 10 for a definite "case" of clinical anxiety or depression. However, Wood et al (1992), found a significant difference in HAD depression scores between current (6.2±2.7) and recovered (3.1±3.3) CFS patients, with a non-significant difference in HAD anxiety scores. In the current study, improvement was not associated with a decrease in the HAD depression or anxiety scores. In addition, no significant changes were observed in the PSQI score during either treatment, again because sleep quality was at the lower end of the scoring range (0 - 21) at baseline and also because those with sleep disorders were successfully treated prior to entry into the trial (Buysse et al, 1988). Alternatively, it could be that exercise may improve subjects' fatigue and functioning without altering mood or sleep quality.

Another treatment study with CFS patients compared the effects of 16 weeks (21 sessions) of cognitive behaviour therapy (CBT) with normal medical care. Outcome measures included a 6 minute walk test, HAD scales for depression and anxiety, visual analogue scales of fatigue, CGI scores and the Karnofsky scale of capacity (Karnofsky et al, 1948) over the previous month (Sharpe et al, 1996). They found that 27% (versus 20% of controls) made a significant improvement by 5 months (immediately after completing treatment) with CBT, compared to 52% who were better with the exercise treatment in the current study, assessed 2 months

earlier. At final follow up, outcomes were similar with 70 per cent of patients rating themselves as "improved" with CBT (at 12 months), which compared with 76 per cent with exercise therapy. However, treatment outcomes were not the same, with the CBT study concentrating on functional rather than symptomatic improvement. It is interesting that the CBT treatment was associated with a delayed emergence of a psychotherapeutic effect over the follow-up period. The authors suggested that the improvement resulted from changing patients' assumptions and maladaptive coping patterns. Deterioration, noted as a rating of "worse" or "much worse", was reported by 13% in the CBT group and 10 % in the medical care only group, which is higher than with exercise in the current treatment study, whereby only 1 patient (3%) considered themselves worse with exercise treatment. A recent study compared 13 sessions of CBT with relaxation therapy carried out over 6 months in a group of 60 CFS patients, with a greater perceived physical incapacity (Deale et al, in press). At 6 months 28% vs 7% were no longer fatigue cases, while at final follow-up 1 year after treatment onset, 70% on CBT and 19% on relaxation treatment achieved a "good outcome" (a substantial improvement in physical functioning).

Both CBT studies treated subjects with concurrent psychiatric disorders. It may be that CBT would be equally as effective as exercise treatment in the absence of co-morbid disorders. Further research should compare the different treatments and also explore their combination. Similarly to the current study, Deale et al (in press) used relaxation therapy as a control treatment, whereas Sharpe et al (1996) compared CBT to normal medical care. However, a reason for the large eventual difference between treatments in the latter study could be the lack of active treatment in the medical care only group, who were given a diagnosis, advised to increase their activity level and referred back to their GP. The control treatment in the current study was considerably more active, with the same amount of patient contact time and advice given, which may explain the improvements seen in this group. This also further emphasises the exercise treatment as being more effective, not just than waiting list control or vague one-off advice, but than a matched treatment with regard to time, attention and feedback. Additionally, Guthrie (1994) has cautioned that the absence of control for the non-specific effects of psychotherapy raises certain doubts regarding the claimed specificity of

treatments. Wilson et al (1993) had previously found that no additional therapeutic effect was obtained from CBT in comparison to good clinical care characterised by illness explanation, education, validation of symptoms and support form health professionals.

It can only be speculated on how important it was to treat or exclude subjects with psychiatric disorders or sleep disturbance. Treatment success was independent of both psychological and sleep improvements. The only subjects to feel worse after completing treatment had both developed depressive illnesses. The present evidence suggests that these maintaining factors should be treated before embarking on an exercise programme. Because of the nature of the illness and the duration, it is understandable that a significant proportion of patients may develop a minor psychiatric disorder, particularly depression, and unless this is treated alongside or prior to the exercise or CBT treatment, it would be difficult to be specific about the outcome. In this respect, it could be that a patient suffering from depression may improve physically and overcome many of the fatigue symptoms, but they may be incapable of recognising this due to a low self-esteem and continued depressive mood. Treating the depression separately, allows us to examine the effects of exercise on the fatigue syndrome itself, while allowing patients to experience and recognise these improvements. Most of the previous research on the psychological effects of exercise has examined its use with anxiety and depression, and it would be unreasonable to presume that an exercise programme alone could be the most effective treatment for more complicated psychiatric disorders, such as hysteria, phobias and eating disorders. Therefore, patients suffering from mild depression or anxiety, of the type that may result from a long-term illness, in addition to chronic fatigue, could be expected to respond positively to the type of programme outlined in this study, but those with major psychiatric disorders, such as those mentioned above should be treated appropriately beforehand.

A comment must be made on the improvements observed in the group performing only flexibility and relaxation for the first twelve weeks. No changes were found in their aerobic capacity but their overall exercise tolerance improved. In this respect, the effect of weekly contact and discussions about progress, regardless of the amount and type of exercise

undertaken appears to have had a significant effect on perception of difficulty, confidence and willingness to tackle physical tasks and may have helped them to overcome general fears or anxieties about physical activity. As with Deale et al, (in press), who found that relaxation was not a pure placebo treatment, our comparison group (flexibility and relaxation) also benefited from the sessions, and many patients in the Deale study reported that relaxation aided pain control, sleep and rest, such that the authors suggested that it may be useful as an adjunctive technique in clinical practice. It appears that these changes are independent of improvements in fitness. However, self-rated symptomatic improvements in physical fatigue and physical function and general health were greater following a more strenuous exercise programme. This discrepancy between decreased fatigue symptoms and changes in aerobic capacity was also seen in the cross-over group after three months on the aerobic exercise programme. This was associated with significant improvements in physical fatigue and increased physical function and general health, but with a lesser magnitude of change in aerobic capacity and exercise tolerance than the original exercise group. We know, from their activity diaries, that they recorded the same amount of time exercising as those in the original exercise group, but this may have been at a lower intensity, despite being prescribed target exercise zones, having started with three months of non-aerobic activity

The analysis of the cross-over group, comparing the results after exercise with those after flexibility and relaxation are shown in Appendix E. The changes following the flexibility indicated an improved exercise tolerance revealed by the increased test duration, peak heart rate and peak blood lactate, while the increase in aerobic capacity, indicated by an increased VO_2 peak was only observed after the aerobic exercise programme. This again points to a general increase in lifestyle activity, but not aerobic exercise, during the flexibility treatment, sufficient to improve exercise tolerance and patients' willingness to push themselves. These changes were then increased, although not significantly during the exercise treatment, which was, in addition associated with an increased aerobic capacity. It was not until they crossed-over and completed the exercise treatment that significant changes were observed in physical function and general health and thus their own perceived physical capacity. However, the regular therapist contact and involvement in a physical treatment programme during the

flexibility treatment was sufficient to stimulate changes in social activities and perceived energy levels. In this respect, it is worth pointing out that participation in any activity, no matter how little, has positive physiological and psychological benefits, such that sufferers should never feel intimidated by their low levels of ability to begin with.

Martinsen (1990) also found that an increase in aerobic fitness was not necessary for the psychological benefits of exercise to be observed. Similarly, two studies by Veale et al (1992), examined the effects of moderate and low intensity exercise on depression. They found no significant difference after 12 weeks between the low and moderate intensity exercise on their main physiological measure of estimated VO_2 max, although the value increased in the exercise group. However, they did find significantly lower clinical interview schedule (CIS) score and Spielberger trait anxiety after 12 weeks of the moderate exercise programme. Their second study found no significant differences in CIS scores, Beck depression inventory, or Spielberger trait anxiety, or aerobic fitness between the groups who followed either a aerobic exercise programme or a low intensity programme consisting of stretching, relaxation and yoga. This implies that there is no relationship between change in aerobic fitness and change in observed ratings of mental state and that the therapeutically effective component of the exercise programme was not the improvement in aerobic fitness.

The current study suggests that improvements rely initially on introducing patients to a regular pattern of activity that may or may not be considered of sufficient intensity to stimulate increases in maximum aerobic capacity, but with the aim of gradually increasing the intensity over time as confidence, self-esteem and a sense of control over physical symptoms are achieved. The quantity and quality of exercise needed to obtain health-related and positive behavioural effects may differ from that which is recommended for fitness benefits, particularly in patient groups. Although the objectives of the exercise programme are to reduce fatigue and to reverse the deconditioning effects, the initial low levels of activity and very gradual progression, may have stimulated relatively small increases in physiological capacity, while allowing larger improvements in symptoms. Psychological improvements with exercise training can occur when submaximal cardiorespiratory fitness improves, despite

no change in VO_2 max. (Cramer et al, 1991), which agrees with our findings of continued and maintained improvement, in the form of decreased HR and RPE, at submaximal levels.

It must be pointed out at this stage that, the aim was not solely to examine whether the physical fitness levels of CFS patients could be improved through a prescribed aerobic exercise programme. Improvement of exercise tolerance was utilised as a means of reversing the physiological deconditioning associated with this illness (shown to be true in the first part of the study through comparison with healthy sedentary controls). Therefore, as a treatment study, the main aim was to examine the efficacy of the given treatment in relieving the symptoms of the illness. Given the nature of CFS, any successful treatment would be expected to have both physiological and psychological effects. Therefore, the target would have been to find the minimum amount of exercise, to achieve a small improvement in exercise tolerance or fitness, while also promoting improvements in self-confidence and self-esteem and symptom reduction. This would, in turn, encourage adherence to the programme, by the very nature that it is perceived as manageable to the patients. These objectives were certainly reached if we consider the CGI scores and the low drop-out rate as reliable indicators of effectiveness of the treatment, particularly from the patients' perspective, which must, after all, be of prime importance in any treatment study.

The use of exercise in the treatment of CFS has been criticised in the past due to reports of patients experiencing a "relapse" of severe symptoms following exercise (Gibson et al, 1993). However, McCully et al (1996) found only 1 out of 16 CFS patients had a significant relapse after a maximal treadmill exercise test, lasting 30 to 40 minutes. In the current study, some patients occasionally reported a resurgence of symptoms but these were not necessarily associated with increases in activity. At these times the volume of activity was decreased, until symptoms regressed. McCully suggested that the trigger for a relapse is not simply a bout of strenuous exercise, but that other factors are involved. In retrospect, it is true that those patients who did experience a relapse, or resurgence of symptoms, usually reported that they had taken on more than normal, physically, psychologically or by way of home pressures/ activities, in the preceding one or two weeks.

To further examine the efficacy of the exercise treatment the results of all those who had followed the exercise treatment programme (original exercise plus cross-over groups) were pooled together and analysed. The significant improvements over baseline in almost all physiological measures and most symptomatic measures in the total group of 51 CFS patients, after exercise, lends further support to the value of this type of treatment for this condition. As mentioned previously, the lack of change in measures of mental health suggest that effective treatment is independent of antidepressant or anxiolytic effects. Although the PSQI total score at baseline did not identify any significant sleep disturbance, regular participation in the exercise programme had significant positive effects on sleep quality and quantity, as has been previously reported (O'Connor & Youngstedt, 1995). Therefore, pooling the data of all those who completed the exercise treatment indicated that, regardless of starting group, CFS patients respond positively, through both physiological adaptations to exercise, and associated improvements in the main symptoms of the syndrome. These affects were measurable after just 3 months on a regular and moderately intense aerobic exercise programme.

Follow-up: 3 month and 1 year

The most significant result at follow-up was that the CGI scores continued to improve which indicates the patients' own rating of how much they have recovered. Sixty-seven and sixty-nine percent of those in the flexibility (and cross-over) and exercise alone groups, respectively, rated themselves as at least much better at 3 months. Even more positively, 74% of the CFS patients who had followed the exercise programme had the same rating a year later. and Those who had followed the exercise programme only, had maintained all of the physiological improvements at follow-up, three months after completion of the supervised programme, although the VO_2 peak had decreased slightly. Those who began with flexibility, and crossed-over to exercise, maintained most of the physiological changes measured post-exercise, except VO_2 peak and maximum ventilation. As an observation, this group tended to place a lot of emphasis on the flexibility training throughout their exercise

programme and this was occasionally substituted for a more strenuous session, when they felt fatigued. Also, since they had a more gradual introduction to exercise, starting with 12 weeks of stretching and relaxation, they may not have exercised as strenuously as the exercise group, particularly in the period between completion of the trial and follow-up, when the amount of exercise they did was at their own discretion. They continued to exercise, but possibly at a lower intensity, which was sufficient to maintain improvements at submaximal levels, but not in maximum aerobic capacity.

Improvements in Chalder and V/A fatigue scales were maintained in both groups at follow-up, whereas the Barsky score was improved only in the cross-over group compared to baseline. This measure indicated a decreased tendency towards amplification of bodily symptoms and an increased threshold for pain, which complimented the increased exercise and lactate tolerance. Somatic amplification, along with symptoms and discomfort, have been shown to be significant predictors of impairment of functioning (e.g. curtailing of daily routine, work or social activities) (Barsky et al, 1988). Increased attention to internal cues results in greater perception of fatigue and physical symptoms (de Coverly Veale, 1987) and it may be that the exercise provided a distraction from increased attention to bodily symptoms. In short, these measures indicated that patients continued to experience a decrease in the predominant symptom of the illness and the symptom that they were most likely to notice or complain of, i.e. fatigue. This may have been associated with less awareness or attention to the illness symptoms as a result of changed habits and renewed interests in other activities.

Those who had followed the exercise programme alone, showed increased social function, emotional role and total SF36 score indicating that they felt that any physical or emotional problems were less likely to interfere with social activities, and that they no longer felt that emotional problems interfered with work or daily activities. This would imply a general trend towards a greater feeling of control. Those who followed the flexibility and then the exercise programme showed significantly greater capacity for social and physical activities, which were less likely to be restricted by their health, and an improved feeling of calm. After either

treatment, patients were more inclined towards resuming normal social and physical activities and lifestyles. Emotional/mental improvements in both groups further illustrated the effects of regular aerobic exercise on psychological well-being, in addition to the well-documented effects on physiological capacity. The cross-over group, in particular, chose to continue exercise at a lower level, which was sufficient to reduce their fatigue symptoms, but was below the level necessary to maintain the previous improvements in maximum aerobic capacity, although other physiological improvements were maintained. Improvement in submaximal exercise tolerance is more relevant to maintenance of daily activities and functions.

In the same way as we pooled together the results of all those who had completed the exercise treatment, we pooled the 3 month follow-up results of all those patients who had completed the exercise programme and attended for follow-up. This gave very similar results as the pooled data post-exercise results immediately after treatment with all physiological improvements being maintained at 3 months, and all measures significantly improved compared to baseline (Table 4.21). The maximum aerobic capacity of the total follow-up group had decreased slightly, compared to immediately after the exercise programme, but this value was still significantly greater than baseline. General exercise and pain tolerance were also maintained, indicated by the increased test duration, peak heart rate and peak blood lactate results, as was also shown by the results immediately after the exercise programme. Submaximal exercise response and strength, which may have a greater bearing on general functional capacity, were also maintained. In addition to the reduction in perceived exertion and heart rate levels observed on completion of the exercise programme, oxygen uptake was also significantly lower at all submaximal test stages (between 4 and 12 minutes) (Figure 4.8). In this respect, short term adaptations to regular exercise caused a lowering of the exercise heart rate and a subsequent reduction in RPE, a combined physiological and psychological effect, whereas a greater efficiency of oxygen extraction and consumption and improved economy/efficiency of effort may be considered to be more longer term adaptations, and thus, were not observed until they had participated in regular exercise for a longer period. It is possible that at this stage we are beginning to observe the effects of an

increased stroke volume, without the relative tachycardia that was necessary in the previous assessment, to maintain the cardiac output. All of the symptomatic improvements, were maintained or improved upon. Therefore, once patients had established a regular exercise routine and experienced the associated improvements in physical and symptomatic levels, they continued with the exercise, albeit at a lower level, but one which was sufficient to maintain improvements.

A further confirmation of the efficacy of exercise treatment can be seen by comparing these pooled results at 3 month follow-up with the results of the healthy sedentary controls assessed for the baseline comparison. This could determine if, in the short term, CFS patients who showed significant deconditioning initially, actually reached similar fitness levels to a healthy sample from the general population, following a tailored exercise programme. With this comparison, absolute peak VO_2, maximum ventilation, maximum heart rate, peak blood lactate and test duration all reached levels similar to those measured in the sedentary control group. Leg strength did not improve to these levels, which is not surprising due to the absence of specific strength training during treatment. Although one could argue that the control group, being sedentary, had a fitness level below the optimum, it must be remembered that they represented a group of healthy individuals with no recorded difficulties in maintaining "normal" lifestyles, nor with any major complaints of fatigue. If the CFS patients were to continue with a regular activity programme, even at a lower level than during treatment, we could expect further improvements in fitness towards optimal levels, particularly with regard to leg strength. However, although all of the symptomatic measures increased significantly compared to baseline, they did not reach the same levels as those measured in the control group on most scales. The two measures that did improve to these levels were mental health and emotional role. Therefore, although patients felt much improved after treatment, confirmed by 68% scoring 1 or 2 on the self-rated CGI scale, their score on measures of fatigue, physical function or general health had not returned to levels that might be considered healthy or normal. However, six or nine months is a relatively short period of time in relation to the average illness duration of over 3 years. In many patients, the main barrier to physical treatment, may have been a perceived low physical

capacity and fear of worsening their symptoms. Therefore, one could reasonably expect changes in these parameters to take longer, while patients have to adapt their whole attitude to activity and their ability to deal with physical tasks that have remained a potential barrier or potential cause of relapse for such a long time. Physical changes can probably occur in spite of individual beliefs and/or confidence levels, if they increase their activity levels, wheras psychological changes, particularly in terms of long-term attitudes and perceptions, may take a lot longer to alter.

There have been criticisms that CFS patients, despite initial improvements, tend to relapse several months after a treatment programme and that the general long term prognosis does not indicate a good recovery rate. In a 3-year follow-up study of 103 CFS patients, only 6 recovered fully and 20% could not perform substantial physical activity (Wilson et al, 1994). Kroenke et al (1988) found that only 28% of patients with chronic fatigue improved after 1 year. In the current study, we followed-up CFS subjects 1 year after completion of the programme (15 or 18 months after trial entry, depending on initial treatment group). The percentage rating themselves "much" or "very much better " had increased to 74%. This result, together with a general trend towards a return to work or study and a continuation of activity, indicates a very positive long-term effect for this type of treatment. It is far more significant than any improvement that might have occurred spontaneously in the absence of this intervention, taking these previous follow-up studies into account (Wilson et a, 1994; Kroenke et al, 1988). There was a moderate increase, from 18% up to 26%, in the number working or studying part-time and more substantial increase, in those returning to full-time employment or education (20% up to 40%). This may reflect the general trend towards a resumption of normal lifestyle, beginning with part-time and moving towards full-time employment. It would be interesting to follow the group up 1 year later, to determine if a significant number of those working/studying part-time had substantially increased their hours or returned to full-time employment or education.

Bombardier & Buchwald followed a group of CFS patients one and a half years after initial assessment, during which time several patients had tried antidepressant medications. Sixty-

one percent had improved a little but few had returned to premorbid levels (fully recovered), with 11% resuming full-time and 13% resuming part-time work. This is considerably lower than the 66% working/studying full- or part-time (40%full and 26% part-time) after treatment, in the current study/. This represents a 27% increase from the proportion working/studying at baseline (39%) (25/66). Wilson et al (1994) found that 50% of CFS patients, followed up 3 years after initial assessment, some of whom had enrolled on an immunoglobulin treatment trial, reported some improvement. Only 6% of this group considered themselves completely recovered, with 20% unable to do any form of physical activity and 40% unable to maintain any social activities. We reported that 68% of those patients followed up a minimum of 18 months after initial assessment still considered themselves regularly active, which, interestingly, was significantly higher than the 55% who considered themselves regularly active prior to the illness. In this respect, some individuals, who had not been involved in sport or any regular activity for some years, even before developing CFS, reported a renewed interest, either through noticing improvements in fitness levels or feeling more confident when appropriate guidelines were given.

Recovery rates (41%) were slightly better in a two and a half year follow-up study, which also used the SF36 health survey questionnaire to assess mental health (50.5 (21.8) vs 61.3 (14.4)) and physical function (36.3(29.6) vs 44.8(30.3)) at baseline and at follow-up, respectively (Clarke et al, 1995). Baseline values were somewhat lower in both measures than those in the current study, probably due to our exclusion of psychiatric disorders in the case of the mental health measure. Although assessed only up to 6 or 9 months after initial baseline measurements, the exercise treatment was associated with a 56% improvement in physical function, compared to 23% in Clarke's study. At 4 year follow-up, during which time cognitive behavioural therapy, with or without antidepressants, was available, 50% of a group of 29 CFS patients considered themselves recovered or almost recovered, while 64% of those who had accepted and completed treatment (14/22) reported a sustained improvement at 4 years (Bonner et al, 1994). Overall, the long-term results from the current exercise treatment study, show a sustained improvement and maintained recovery rating on the CGI score, which exceeds long-term outcomes of other treatments, such as antidepressants or

immunoglobulin therapy. The only other treatment that has been shown to have comparable long term positive outcomes is CBT. It should be noted that both of these approaches, exercise and CBT, involve lifestyle changes and subsequent attitude/belief changes, which are absolutely essential for the long-term effectiveness of treatment. The main difference is that CBT actually works directly on changing attitudes to the illness and its symptoms, whereas these changes tend to occur as a consequence of participation in a tailored graded exercise treatment programme. However, it should also be noted that regular contact and discussion with the exercise physiologist may also act as a form of CBT.

One of the limitations of the current study is that the follow-up can only be extended to 18 or 21 months after initial assessment, but it would be interesting to examine the long tern outcome of CFS patients completing an exercise trial for an extended period as other studies have reported (with little or no treatment offered). All of the reported follow-up studies included patients with current psychiatric disorders and all reported these to be strongly associated with incomplete or no recovery. Indeed, Wells (1989) reported that affective disorders seem to play a significant and independent role in determining functional outcomes among a wide range of chronic medical conditions, again justifying the approach of treating these before embarking on a physical treatment programme.

How, then, did the exercise treatment work? It was independent of mood and sleep changes, was associated with increased aerobic capacity, strength, exercise tolerance, and reduced perception of effort. I believe that success depended on both a physiological training effect and a graded exposure to the feared stimulus of physical activity. Perception of effort significantly improved with exercise, suggesting further research should examine perceptual, as well as physiological, responses to exercise. It was also shown that CFS patients differed from the depressed group, who were equally as unfit, in their perception of physical function and role. This may again be one of the barriers that are broken down by exposure to a physical treatment. It was stressed at all times that it was more important for them to slow down and to continue exercising for the entire period than to adhere to a faster pace for shorter periods. People who may have been inactive for a long time are inclined to do too

much too soon, and then give up, and this seems to have been the previous approach of many of the CFS patients who had tried exercise. They were encouraged to listen to their own body and to slow down, rather than stop, if the exercise felt to difficult to continue. This ultimately results in faster improvements in fitness than more intense, but less continuous exercise. It also makes the exercise more enjoyable and encourages patients to monitor their own progress. By following-up patients 3 months after treatment completion, during which time they were told how to maintain and progress their exercise, they were given the control to choose the level comfortable for them, while also knowing that they could seek advice if needed. Indeed, Deale et al (in press), suggested that treating patients until they reach optimum functioning may be unnecessary. Outcomes could be enhanced by treating patients until they take over responsibility for their treatment and they could then be followed up with "booster" sessions.

The results presented in this study suggest that <u>appropriate</u> exercise, whereby careful monitoring and planning is gradually handed over to the patients, has an important role to play in the rehabilitation and recovery of patients with CFS. Because of the low level of exercise tolerance in this group, such an exercise programme needs to begin at a low intensity, whereby regularity, rather than volume, is the goal. Progression should be very gradual, aiming for a general increase in daily activity, using an exercise regimen resembling that for the unimpaired, but adapted in duration and intensity. Patients should avoid "overdoing it" during the good phases of the illness but also they must try to continue the activity pattern, albeit at a reduced intensity, during the relapse phases. The key to recovery must be through regular and moderate activity. The results show that it is possible to change the course of the illness by minimizing the deconditioning process and by keeping patients at an optimal level of physical functioning, through an exercise prescription designed for the individual patient. Regardless of amount and intensity of exercise, the importance of a regular routine and taking positive action cannot be over-emphasised.

The combination of approaches described in this study allows us to look at the different treatments alone and, with the cross-over group, a combination of treatments. Taking into

account the results of the cross-over group, it appears that the most important aspect is the participation in regular physical activity, no matter what type or how little, is the important starting point. The psychological changes associated with only small improvements in traditional measures of fitness, indicate the value of regular positive reinforcement (therapist contact), attention and guidance, in changing the patients own perception of physical ability and their willingness to tackle and control certain aspects of their illness. Exercise or activity, of any type, is a method of treatment that they can understand and can control themselves, which can ultimately lead to an increased confidence and self-esteem, while also allaying general fears about physical tasks. The first target is getting them to do enough activity to overcome that initial barrier, and only after this is achieved will they be happy to carry on and progress.

4.4 Limitations of the study

The nature of the study, involving an initial treadmill walking test, as well as weekly visits to the laboratory, excluded those who were more severely disabled, who would not have managed the travel or the assessment itself. Therefore, the treatment described in this study would not be applicable to those CFS patients who are either bedridden or wheelchair-bound. However, all exercise prescriptions are adaptable and suitable exercises could be devised for such patients, taking into account their restrictions, with a view to improving their function very gradually to the stage whereby they could begin a low intensity aerobic exercise programme. This may have to be carried out through an in-patient programme.

Throughout the study the exercise physiologists were not blind to the treatment group of the patient. Initially, there was only one physiologist involved, but after the first six months, there were always two, aiming to alternate the person with whom the patients did their exercise sessions to avoid bias or attachment to one therapist. Also, care was taken to standardise the protocols and any verbal encouragement given to all patients during their physiological assessments. Patients were also informed that the those carrying out the study were assessing both treatments, either of which could be more effective and there was no contact between the patients while on the different treatment programmes. To reduce bias,

the main outcome measure, the CGI score, was carried by a psychiatrist who was blind to the treatment group.

It may be considered more complete if the protocol had allowed those patients who completed the exercise treatment first to cross-over into the flexibility programme, as the other group did. However, this would have been difficult to put into practice, since patients once introduced to a regular aerobic exercise programme, would probably have continued with a lesser amount, even if they were instructed to avoid aerobic exercise. We also wanted to assess the effects of an exercise programme alone, from baseline to follow-up. In addition, the nature of the cross-over protocol meant that there was no 3 month post-treatment assessment for those who had followed the flexibility programme alone, as the majority of those who had completed the flexibility took up the option of joining the exercise programme. In an ideal situation, perhaps they should not have been given this option. However, when the aim of the treatment is to improve both the patients' symptoms and their overall perception of improvement, it would be very difficult and, indeed unfair, to deny them the option to take part in a treatment programme which was associated, from an early stage, with better improvements – particularly in terms of the CGI score.

Due to that fact that those following the flexibility programme did not use heart rate monitors, we did not know if their heart rate was sufficiently elevated during their stretching sessions to cause a training effect. This, and the fact that, once part of an active treatment programme, they tended to become more active in general and to take on previously avoided physical tasks, despite being instructed to avoid aerobic activities, may explain some of the improvements found in this group following the flexibility programme.

Given the high prevalence of psychiatric disorders in CFS patients, exclusion of this group or treatment prior to entry restricts the application of the results to CFS patients without a psychiatric disorder. However, since a psychiatric diagnosis has been shown to have strong effects on outcome and recovery, this exclusion was necessary in order to assess the effects of the exercise and flexibility treatments on CFS alone (as was discussed previously). It was

interesting that the two patients who reported feeling worse after treatment were both suffering from a depressive illness when assessed. This lends support to the fact that psychiatric disorders should be treated prior to the exercise programme and this would be continued throughout, possibly through the implementation of CBT alongside the exercise programme.

Despite these limitations, this study has confirmed that individually tailored and graded exercise therapy has an invaluable role to play in the treatment, with regard to both physiological and symptomatic improvements, and long-term recovery of patients with chronic fatigue syndrome. The nature of any study dealing with patients and examination of the efficacy of various treatments, inevitably implies that some compromises may have to be made in terms of the protocol, to ensure that the patient care and their access to appropriate treatment, is considered first and foremost. In this respect, some of the limitations could have been avoided, such as control of the flexibility group activity, but others, particularly in terms of design of the study, such as the cross-over protocol, were a necessary compromise for the care of the patients involved. Nonetheless, the results still leave no doubt as to which treatment is associated with a greater overall improvement in physical and psychological symptoms.

It could be argued that CBT is potentially as effective a treatment, and indeed, the results of both treatments are very similar after one year. The very nature of both treatments implies that there are similarities in that should compliment each other. Both incorporate recommendations to increase activity, to a greater or lessor extent, and both employ a certain degree of patient therapist contact, discussion and counselling. To date most studies using CBT have included patients with co-morbid psychiatric disorders, which prevents a direct comparison. In the future, the next step should be to compare both CBT and graded exercise therapy with the same type or group of CFS patients. However, it could reasonably expected that graded exercise would emerge as equally, if not more, effective in patient improvement and long-term maintenance of improvement, while also suggesting that CBT has an important role to play in dealing with CFS. Physiological improvements associated with CBT take

longer, but these are ultimately the improvements that patients tend to notice first, as they begin to cope with physical tasks and activities better, allowing them to resume social and daily activities, which are important to them. In terms of patient rating of improvement (CGI score), there is no doubt that graded exercise therapy has been shown to have the most positive long-term outcome in improvement in the symptom of CFS than most other treatments to date.

As a follow-on from this study, practical guidelines with details on the implementation of a graded exercise programme with CFS patients will be produced. This will be in a format applicable to doctors, physiotherapists, nurses and cognitive behavioural therapists. This type of approach, also has applications in the treatment and rehabilitation of several chronic medical conditions and it is hoped that we will continue to apply a similar format to further research in these areas in the future. Having considered all of these results, there is a very clear evidence that graded exercise therapy is an effective and invaluable treatment in facilitating the recovery of patients with Chronic Fatigue Syndrome.

CHAPTER FIVE: SUMMARY AND CONCLUSIONS

The initial comparison between a group of CFS patients and a healthy sedentary control group revealed that individuals suffering from CFS have a significantly reduced level of physical fitness as measured by a significantly lower peak aerobic capacity, pain tolerance, exercise tolerance and strength, and a higher perception of exertion at submaximal levels of intensity. It must be stressed that CFS patients were compared to a healthy, but inactive, control group, and the fact that they had a significantly lower fitness level than this group, confirmed that they were, indeed deconditioned. The CFS group exhibited detraining effects that could be associated with a very inactive lifestyle, and a perceived inability or a barrier to tackling physical tasks. Due to this reduced physical function and associated physical and mental fatigue, the CFS patients had restricted their lifestyles and social lives to cope with this long-term illness. We could expect that this had consequential effects on mood and emotional health. Despite exclusion of CFS patients with psychiatric disorders, these groups were significantly different on measures of physical and mental fatigue, general health, social and physical function and bodily pain compared to the control group. These symptoms are, therefore, due to the illness rather than depression, particularly as clear differences emerged when the CFS patients were compared on the psychological measures, with a small subgroup of depressed patients. The CFS group studied were typical of CFS patients in general, in terms of duration of illness, gender distribution, employment and causal attribution. Therefore, it is reasonable to assume that these results can be generalised to other patients with CFS. These patients were indeed out of condition, weak and fatigued, all of which are parameters that could potentially be improved, if not reversed, through a gradual return to activity and an attempt to break the circle of inactivity, decreased exercise tolerance, frustration, further activity avoidance and depression.

Participation in a carefully controlled, graded aerobic exercise programme was associated with improvement in aerobic capacity, exercise tolerance, submaximal exercise capacity, efficiency and strength after three months. Smaller changes in exercise tolerance and no increase in aerobic capacity were observed in CFS patients who followed a similar duration

programme of flexibility and relaxation. This indicates that the aerobic exercise is a more effective treatment, particularly with regard to reversal of the effects of deconditioning associated with this condition. Further evidence of the efficacy of this treatment was shown by the similar improvements measured in those who crossed over to the exercise treatment following the flexibility programme.

Important positive symptomatic changes included improved general health, decreased physical and mental fatigue, increased vitality, physical and social function, which improved to a greater extent with the exercise treatment. The patients' overall rating of improvement on the CGI scale, which was significantly better with exercise (55% vs 27%), further confirmed this. This scale is an important objective (from the therapists point) and subjective (from the patients perspective) measure of the overall effectiveness of the treatment. The value of such a scale, which involves the patients'own estimation of improvement has been discussed. One of the most important criteria in a treatment trial has to be whether the patients or subjects feel the benefits or effects, and this was successfully demonstrated throughout this study. After all, what must be considered to be most important, is whether the patients themselves feel that they have improved and are continuing to recover from Chronic Fatigue Syndrome.

The long-term outcome of the treatment also indicated that these improvements, both physiological and symptomatic, were maintained, and, in some measures, exceeded. More importantly, the patient rating of improvement also increased (68%) at follow-up, three months after completion of the treatment. Longer term follow-up indicated a continued improvement in symptoms, whereby three-quarters (76%) of those who completed the exercise treatment considered themselves "much" or "very much better" a year after completion, with a general trend towards a return to work or study and a maintenance of a regular activity programme by the majority. This is a very important long-term health, symptomatic and lifestyle change, which must be considered a very important improvement.

Compared to other trials, this study represents a more holistic improvement in symptoms and physiological effects and a greater treatment effect, which was maintained. Wilson et al (1994) commented that there have been notably few double-blind, placebo-controlled studies in adequately defined patient samples in CFS treatment research, and this study, although not double-blind, does represent a step towards bridging the gap. They also suggested that the absence of objective response markers has also meant that the outcome of many studies has relied on highly subjective measures, whereas the current study employed a combination of subjective and objective symptomatic measures and objective physiological measures to assess treatment outcome.

Future studies should examine the combination of CBT and exercise, since CBT alone has also been shown, in the more recent trials, to be associated with a similar rate of improvement in CFS patients. Recommendations on increasing daily activity levels are frequently included in CBT treatment such that the more comprehensive approach to treatment could include the combination of psychological (CBT) and physiological (exercise) programmes supervised by the relevant professionals working together. Indeed, Deale et al (in press) incorporated a planned graded activity programme with CBT, involving activities such as walking and gardening. Patients were encouraged to persevere with their targets and not to reduce them on a bad day or not to exceed them on a good day, similar to the approach in the current study. They considered graded activity to be the key component in the study, making it more successful than some previous CBT trials that excluded exercise (Freidberg & Krupp, 1994).

With regard to future recommendations and the use of this treatment with CFS, the next step could be to examine application within an NHS setting, carried out through a physiotherapy department, but supervised by an exercise physiologist. This should also employ an integrated approach including collaboration with other therapists. Monitoring and control should gradually be handed over to the patient, with a decreasing frequency of visits and clear explanation on progressive exercise. Baseline and post-treatment measures should be taken; utilising whatever monitoring equipment is available, so that programmes can be individually

tailored and improvements can be objectively assessed. When full metabolic/gas analysis equipment is not available, heart rate monitoring during and after progressive walking, cycling or step tests would be sufficient, with/without estimations of aerobic capacity, if required. Symptomatic measures should also be taken using appropriate and validated scales. The programme should ideally begin with regular, low-intensity, aerobic exercise and should include exercises to improve flexibility, while basic strengthening exercises should also be incorporated at a later stage focusing on the legs (mainly the quadriceps) and the upper body (particularly for the muscles involved in lifting and carrying). In some cases, it may be more appropriate to begin with one or two weeks of predominantly flexibility exercises and a focus on increased daily activity, and then progress towards prescribed aerobic exercise. A lot of control of the programme can be eventually handed over to the patient, with proper education, such that visit frequency can be gradually decreased. Analysis needs to be carried out on cost, frequency of visits required, optimum duration of contact sessions, equipment required, number of patients that can be treated together, referral structure and patient suitability.

Ultimately, this treatment would work out more cost effective than expensive drug treatments, which have not proven to be reliably or uniformly effective to date. In order to facilitate this approach, general practitioners need to be alerted to the prevalence of chronic fatigue syndrome and how to recognise it, such that patients can access treatment more readily. Literature and guidelines could be available to them on the implementation of exercise in the treatment of CFS such that the programme could begin through the practice under the guidance of appropriately trained personnel, with a view to linking up with a local physiotherapy or exercise physiology department when available. Major psychiatric disorders should be treated prior to entry to an exercise programme, as there is evidence that these have separate effects on outcome.

There is no doubt that graded aerobic exercise, appropriately tailored to individual conditions, has an invaluable role to play in the treatment of, not only CFS, but also, potentially, several other chronic conditions, which are also associated with deconditioning.

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APPENDIX A

Chronic fatigue syndrome - Holmes et al (1988)

A case of CFS must fulfil major criteria 1 and 2 as well as the following minor criteria: either 8 or more of the 11 symptoms or at least 6 of the 11 symptoms and at least 2 of the 3 physical signs specified.

Major criteria

1. The onset of persistent or relapsing, debilitating fatigue or easy fatigability in a person who has no previous history of similar symptoms, which does not resolve with bedrest, and that is severe enough to reduce or impair average daily activity below 50% of the patient's premorbid activity level for a period of at least six months.

2. Other clinical conditions that may produce similar symptoms must be excluded by thorough evaluation, based on clinical history, physical examination and appropriate laboratory findings. Among the specific exclusions is chronic psychiatric disease, either newly diagnosed or previously experienced, (such as endogenous depression; hysterical personality disorder; anxiety neurosis; schizophrenia; or chronic use of major tranquilizers, lithium or antidepressants).

Minor criteria

Symptoms

A symptom must have begun at the time of onset of increased fatigability and must have persisted or recurred over a period of at least 6 months (individual symptoms may or may not have occurred simultaneously).

1. Mild fever - oral temperature between 37.5 degrees C and 38.6 degrees C, if measured by the patient - or chills. (Note oral temperatures of greater than 38.6 degrees C are less compatible with chronic fatigue syndrome and should prompt studies for other causes of illness.)

2. Sore throat

3. Painful lymph nodes in the anterior or posterior cervical or axillary distribution

4. Unexplained generalised muscle weakness

5. Muscle discomfort of myalgia

6. Prolonged (24 hours or greater) generalised fatigue after levels of exercise that would have been easily tolerated in the patients pre-morbid state

7. Generalised headaches (of a type, severity, or pattern that is different from headaches the patient may have had in the pre-morbid state

8. Migratory arthralgia without joint swelling of weakness

9. Neuropsychologic complaints (one or more of the following: photophobia, transient visual scotomata, difficulty thinking, inability to concentrate, depressions)

10. Sleep disturbance (hypersomnia or insomnia)

11. Descriptions of the main symptom complex as initially developing over a few hours to a few days (this is not a true symptom, but may be considered as equivalent to the above symptoms in meeting the requirements of the case definition)

Physical criteria

Physical criteria must be documented by a physician on at least two occasions, at least one month apart

1. Low grade fever - oral temperature between 37.6 and 38.6 degrees C or rectal temperature between 37.8 and 38.8 degrees C

2. Non-exudative pharyngitis

3. Palpable or tender anterior or posterior cervical or axillary lymph nodes (Note :lymph nodes greater than 2cm in diameter suggest other causes. Further evaluation is warranted)

APPENDIX B

PATIENT'S CONSENT FORM

Consultant: P.D. White

Investigator: K. Fulcher

Purpose of the study and brief description of procedure to be carried out:

This study has been designed to answer the question "is gradual rehabilitation with exercise helpful to patients with chronic fatigue syndrome ?".

You will be given a short interview and asked to fill out four brief questionnaires. These ask about tiredness, weakness, sleep disturbance and emotional symptoms. Your muscle strength and physical fitness will next be measured using standard techniques. This will involve sitting in a chair and pushing your right leg straight against a strain gauge. Then you will walk on an exercise treadmill for several minutes at slowly increasing speed and increasingly uphill.

At the same time you will breathe in and oiut of a mouthpiece, so that the level of gases you breathe can be measured. At three separate moments before, during and after the exercise, we shall take a droplet of bleed form your fingertip to measure the amount of lactic acid you produce.

At the same time you will be allocated by chance to one of two treatment groups. In total you will attend here for approximately one hour per week for 13 weeks. In one treatment you will be given stretching and relaxation exercises to do. In the other, you will be given aerobic exercises to do, starting at a low intensity and gradually increasing intensity over the weeks. You will be encouraged to practice the exercises at home on a regular basis.

After 13 weeks your ability to exercise will be measured again in the same way as before. You will also be given the same questionnaires to fill in.

This study has been explained to me and I understand:

(a) What the study involves.
(b) That refusal to participate will not affect my treatment in any way
(c) That I may withdraw at any time.

I therefore agree to take part in this study.

Signature of patient ..... Date .....

I HAVE BEEN PRESENT WHILE THE PROCEDURE HAS BEEN EXPLAINED TO THE PATIENT AND HAVE WITNESSES HIS/HER CONSENT TO TAKE PART

Signature of witness ..... Date .....
(The witness should be a person not connected with the study).

Full name and address of patient:-

.....

.....

.....

APPENDIX C

ACTIVITY QUESTIONNAIRE

1. List any sports or recreational activities that you have participated in during the past three months

	Sport, recreation or other physical activity	Number of times	Average time per episode Hours	Mins
A				
B				
C				
D				
E				

2. Which of the following best describes your lifestyle? (please tick one)

a) I take enough exercise to keep healthy ☐

b) I ought to take more exercise ☐

c) Don't know ☐

3. Considering a 7-day period, how many times on average do you do the following kinds of exercise for more than 15 minutes during your free time?

a) Strenuous exercise (heart beats rapidly) ☐

(i.e. running, jogging, hockey, football, soccer, squash, basketball, vigorous swimming or cycling

b) Moderate exercise (not exhausting) ☐
(i.e. fast walking, tennis, easy cycling, badminton, easy swimming, dancing)

c) Mild exercise (minimal effort) ☐

(i.e. yoga, darts, fishing, bowling, golf, easy walking)

4. Considering a 7-day period during your leisure time, how often do you engage in regular activity for long enough to work up a sweat, get the heart pumping or get out of breath?

a) Often ☐

b) Sometimes ☐

c) Never ☐

For office use

HEALTH STATUS QUESTIONNAIRE(SF-36)

THE FOLLOWING QUESTIONS ASK FOR YOUR VIEWS ABOUT YOUR HEALTH, HOW YOU FEEL AND HOW WELL YOU ARE ABLE TO DO YOUR USUAL ACTIVITIES. IF YOU ARE UNSURE ABOUT HOW TO ANSWER ANY QUESTION, PLEASE GIVE THE BEST ANSWER YOU CAN AND MAKE ANY COMMENTS IN THE SPACE AVAILABLE AFTER QUESTION 10.

Please tick one

1. In general would you say your health is:

Excellent	○
Very good	○
Good	○
Fair	○
Poor	○

2. <u>Compared to one year ago,</u> how would you rate your health in general <u>now</u>?

Much better now than one year ago	○
Somewhat better now than one year ago	○
About the same	○
Somewhat worse now than one year ago	○
Much worse now than one year ago	○

Continued ...

For office

HEALTH AND DAILY ACTIVITIES

3. The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

Please tick one circle on each line

	Yes, limited a lot	Yes, limited a little	No, not limited at all	
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	○	○	○	☐
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	○	○	○	☐
c. Lifting or carrying groceries	○	○	○	☐
d. Climbing several flights of stairs	○	○	○	☐
e. Climbing one flight of stairs	○	○	○	☐
f. Bending, kneeling or stooping	○	○	○	☐
g. Walking more than a mile	○	○	○	☐
h. Walking half a mile	○	○	○	☐
i. Walking 100 yards	○	○	○	☐
j. Bathing and dressing yourself	○	○	○	☐

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Answer Yes or No to each question

	YES	NO	
a. Cut down on the amount of time you spent on work or other activities	○	○	☐
b. Accomplished less than you would like	○	○	☐
c. Were limited in the kind of work or other activities	○	○	☐
d. Had difficulty performing the work or other activities (e.g. it took extra effort)	○	○	☐

For office us

5. During the <u>past 4 weeks</u>, have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

Answer Yes or No to each question

	YES	NO	
a. Cut down on the <u>amount of time</u> you spent on work or other activities	○	○	□
b. <u>Accomplished less</u> than you would like	○	○	□
c. Didn't do work or other activities as <u>carefully</u> as usual	○	○	□

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

Please tick one

Not at all	○	□
Slightly	○	□
Moderately	○	□
Quite a bit	○	□
Extremely	○	□

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	○	□
Very mild	○	□
Mild	○	□
Moderate	○	□
Severe	○	□
Very severe	○	□

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including work both outside the home and housework)?

Not at all	○	□
A little bit	○	□
Moderately	○	□
Quite a bit	○	□
Extremely	○	□

Continued ...

For office us

YOUR FEELINGS

9. These questions are about how you feel and how things have been with you <u>during the past month.</u> *(For each question, please indicate the one answer that comes closest to the way you have been feeling)*

Please tick one circle on each line

How much time during <u>the past month</u>:	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time	
a. Did you feel full of life?	○	○	○	○	○	○	□
b. Have you been a very nervous person?	○	○	○	○	○	○	□
c. Have you felt so down in the dumps that nothing could cheer you up?	○	○	○	○	○	○	□
d. Have you felt calm and peaceful?	○	○	○	○	○	○	□
e. Did you have a lot of energy?	○	○	○	○	○	○	□
f. Have you felt downhearted and low?	○	○	○	○	○	○	□
g. Did you feel worn out?	○	○	○	○	○	○	□
h. Have you been a happy person?	○	○	○	○	○	○	□
i. Did you feel tired?	○	○	○	○	○	○	□
j. Has your <u>health limited your social activities</u> (like visiting friends or close relatives)?	○	○	○	○	○	○	□

For office use

HEALTH IN GENERAL

10. Please choose the answer that best describes how true or false each of the following statements is for you.

Please tick one circle on each line

	Definitely true	Mostly true	Not sure	Mostly false	Definitely false	
a. I seem to get ill more easily than other people	○	○	○	○	○	☐
b. I am as healthy as anybody I know	○	○	○	○	○	☐
c. I expect my health to get worse	○	○	○	○	○	☐
d. My health is excellent	○	○	○	○	○	☐

Comments

Thank you very much for your assistance

Please return the completed booklet in the envelope provided.

NO STAMP IS REQUIRED.

Medical Care Research Unit, Department of Public Health Medicine,
University of Sheffield Medical School, Beech Hill Road, Sheffield, S10 2RX

AMPLIFICATION QUESTIONNAIRE

1/	SUDDEN NOISES REALLY DISTURB ME.	0 1 2 3 4.
2/	I'M VERY UNCOMFORTABLE WHEN I'M IN A PLACE THAT IS TOO HOT OR COLD.	0 1 2 3 4.
3/	I CAN'T STAND PAIN AS WELL AS MOST PEOPLE CAN.	0 1 2 3 4.
4/	I FIND I'M OFTEN AWARE OF VARIOUS THINGS HAPPENING IN MY BODY	0 1 2 3 4.
5/	I'M QUICK TO SENSE THE HUNGER CONTRACTIONS IN MY STOMACH.	0 1 2 3 4.

0 = NOT AT ALL. 1 = A LITTLE. 2 = MODERATELY.

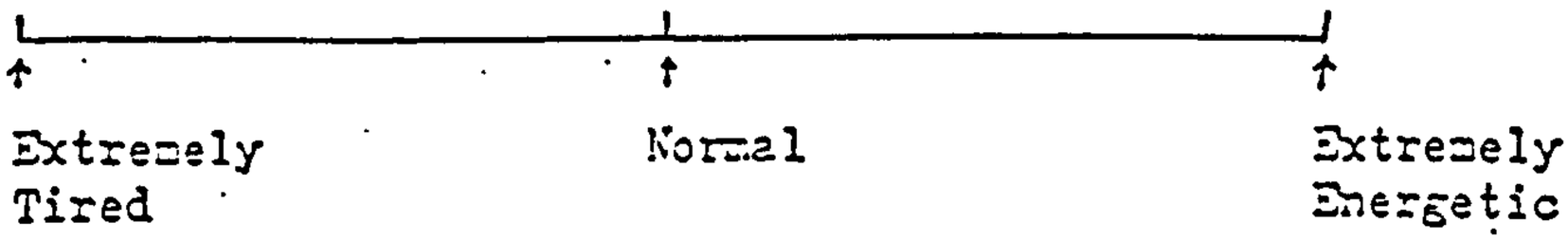
3 = QUITE A BIT. 4 = EXTREMELY.

FATIGUE

I would now like you to judge how tired you have been. Please indicate with a pen for last week, by putting a vertical line where appropriate:

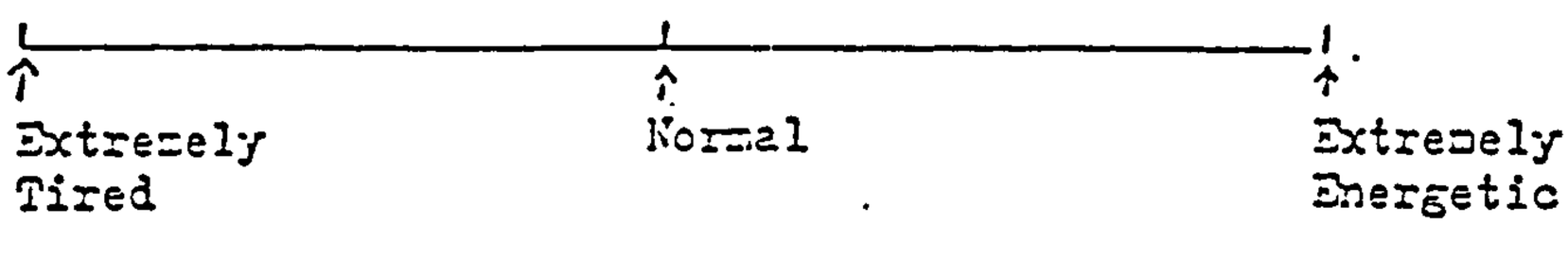
1. PERSISTENT MENTAL FATIGUE

How mentally tired or lacking in mental energy have you persistently felt in the last week?



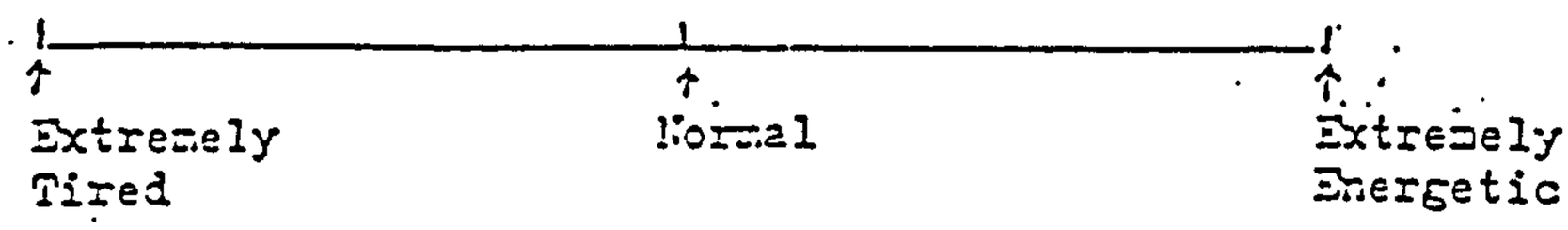
2. PERSISTENT PHYSICAL FATIGUE

How physically tired or lacking in physical energy have you persistently felt in the last week?



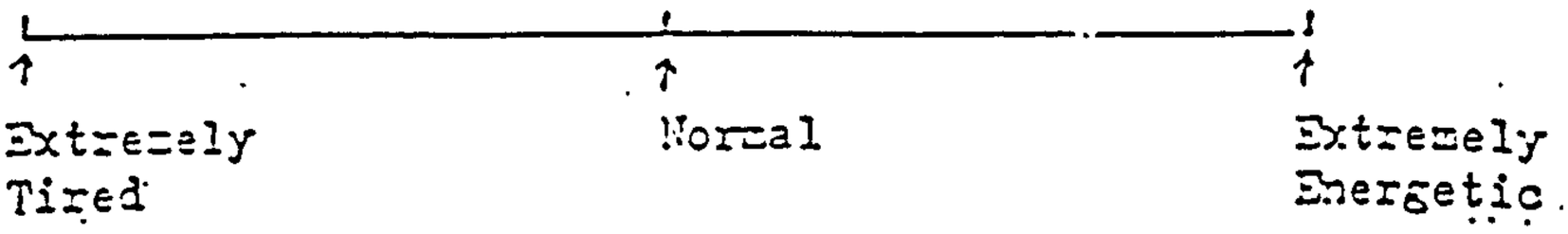
3. EXERTIONAL PHYSICAL FATIGUE

How physically tired or lacking in physical energy have you felt in the last week after physical exertion?



4. EXERTIONAL MENTAL FATIGUE

How mentally tired or lacking in mental energy have you felt in the last week after mental exertion?



TEXT BOUND INTO

THE SPINE

0 2 1 2

ISN M40033

MOCLOBEMIDE VERSUS CLOMIPRAMINE IN FATIGUE AND DEPRESSIVE SYMPTOMS

Patient Number

Please use only BLACK BALL POINT PEN

DO NOT WRITE IN CLOSED BOXES

WEEK 2 CLINICAL ASSESSMENT (continued)
FATIGUE QUESTIONNAIRE

We would like to know whether or not you have been having any problems with feeling tired, weak or lacking in energy in the last few weeks. Please answer ALL the questions simply by underlining or ticking the answer which you think most nearly applies to you. We would like you to answer the questions whether or not you have these symptoms. We would like to know how you feel either *at the moment* or *recently*, rather than a long time ago. If you have been feeling tired for a long time, we want you to *compare yourself to how you felt when last well.*

Do you have problems with tiredness?	Less than usual	No more than usual	More than usual	Much more than usual	☐
Do you need to rest more?	Less than usual	No more than usual	More than usual	Much more than usual	☐
Do you feel sleepy or drowsy?	Less than usual	No more than usual	More than usual	Much more than usual	☐
Do you have problems starting things?	Not at all	No more than usual	More than usual	Much more than usual	☐
Do you start things without difficulty, but get weak as you go on?	Better than usual	Same as usual	More than usual	Much more than usual	☐
Do you have enough energy?	More than usual	No more than usual	Less than usual	Much ~~more~~ less than usual	☐
Do you have enough strength in your muscles?	More than usual	No more than usual	Less than usual	Much ~~more~~ less than usual	☐
Do you feel weak?	Less than usual	Same as usual	More than usual	Much more than usual	☐
Do you have difficulty concentrating?	Less than usual	Same as usual	More than usual	Much more than usual	☐
Do you have problems thinking clearly?	Less than usual	Nor more than usual	More than usual	Much more than usual	☐
Do you make slips of the tongue when speaking?	Not at all	No more than usual	More than usual	Much more than usual	☐
Do you find it more difficult to find the correct word?	Less than usual	No more than usual	More than usual	Much more than usual	☐
How is your memory?	Better than usual	No worse than usual	Worse than usual	Much worse than usual	☐
Have you lost interest in the things you used to do?	Not at all	Same as usual	More than usual	Much more than usual	☐

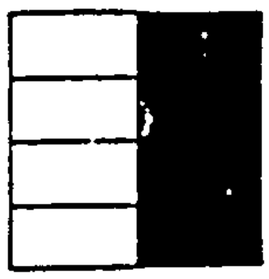
HAD Scale

Name: Date:

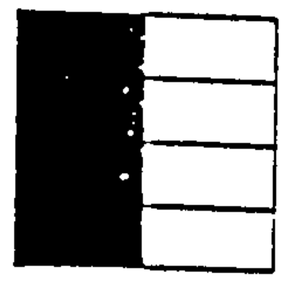
Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he will be able to help you more.
This questionnaire is designed to help your doctor to know how you feel. Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week.
Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

Tick only one box in each section

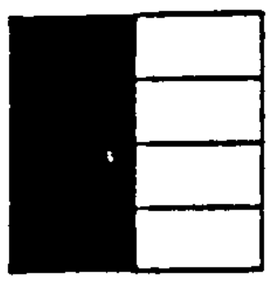
I feel tense or 'wound up':
- Most of the time .....
- A lot of the time .....
- Time to time, Occasionally .....
- Not at all .....



I feel as if I am slowed down:
- Nearly all the time .....
- Very often .....
- Sometimes .....
- Not at all .....

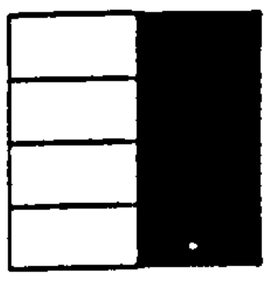


I still enjoy the things I used to enjoy:
- Definitely as much .....
- Not quite so much .....
- Only a little .....
- Hardly at all .....

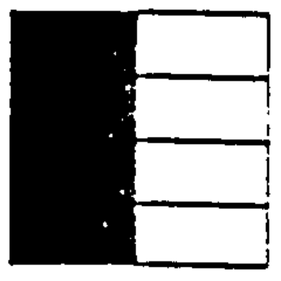


I get a sort of frightened feeling like 'butterflies' in the stomach:
- Not at all .....
- Occasionally .....
- Quite often .....
- Very often .....

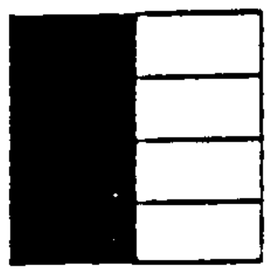
I get a sort of frightened feeling as if something awful is about to happen:
- Very definitely and quite badly .....
- Yes, but not too badly .....
- A little, but it doesn't worry me .....
- Not at all .....



I have lost interest in my appearance:
- Definitely .....
- I don't take so much care as I should.....
- I may not take quite as much care .....
- I take just as much care as ever .....

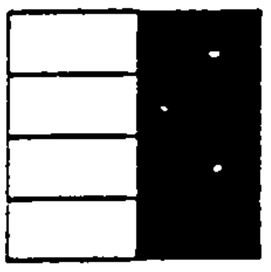


I can laugh and see the funny side of things:
- As much as I always could .....
- Not quite so much now .....
- Definitely not so much now .....
- Not at all .....

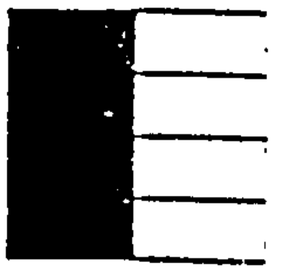


I feel restless as if I have to be on the move:
- Very much indeed .....
- Quite a lot .....
- Not very much .....
- Not at all .....

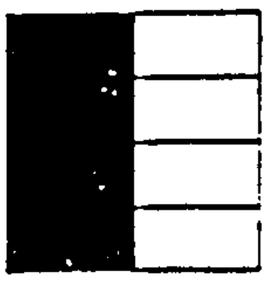
Worrying thoughts go through my mind:
- A great deal of the time .....
- A lot of the time .....
- From time to time but not too often ..
- Only occasionally .....



I look forward with enjoyment to things:
- As much as ever I did .....
- Rather less than I used to .....
- Definitely less than I used to .....
- Hardly at all .....



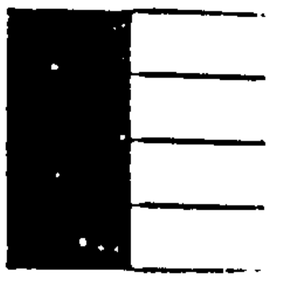
I feel cheerful:
- Not at all .....
- Not often .....
- Sometimes .....
- Most of the time .....



I get sudden feelings of panic:
- Very often indeed .....
- Quite often .....
- Not very often .....
- Not at all .....

I can sit at ease and feel relaxed:
- Definitely .....
- Usually .....
- Not often .....
- Not at all .....

I can enjoy a good book or radio or TV programme:
- Often .....
- Sometimes .....
- Not often .....
- Very seldom .....



Do not write below this line

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AVAILABLE

Variable print quality

Weistein, L.; Dement, W.C.; Redington, D.; and Guilleminault, C. Insomnia in the San Francisco Bay Area: A telephone survey. *Sleep/Wake Disorders: Natural History, Epidemiology, and Long-Term Evolution.* New York: Raven Press, 1983. pp. 73-85.

Appendix. Pittsburgh Sleep Quality Index (PSQI)

Name _____ ID # _____ Date _____ Age _____

Instructions:
The following questions relate to your usual sleep habits during the past month *only*. Your answers should indicate the most accurate reply for the *majority* of days and nights in the past month. Please answer all questions.

1. During the past month, when have you usually gone to bed at night?
   USUAL BED TIME _____
2. During the past month, how long (in minutes) has it usually take you to fall asleep each night?
   NUMBER OF MINUTES _____
3. During the past month, when have you usually gotten up in the morning?
   USUAL GETTING UP TIME _____
4. During the past month, how many hours of *actual sleep did* you get at night? (This may be different than the number of hours you spend in bed.)
   HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer *all* questions.

5. During the past month, how often have you had trouble sleeping because you...
   (a) Cannot get to sleep within 30 minutes

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

   (b) Wake up in the middle of the night or early morning

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

   (c) Have to get up to use the bathroom

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

   (d) Cannot breathe comfortably

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

   (e) Cough or snore loudly

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

   (f) Feel too cold

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

   (g) Feel too hot

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

   (h) Had bad dreams

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

   (i) Have pain

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

(j) Other reason(s), please describe _____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

6. During the past month, how would you rate your sleep quality overall?

Very good ____
Fairly good ____
Fairly bad ____
Very bad ____

7. During the past month, how often have you taken medicine (prescribed or "over the counter") to h you sleep?

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

8. During the past month, how often have you had trouble staying awake while driving, eating meals engaging in social activity?

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm get things done?

No problem at all ____
Only a very slight problem ____
Somewhat of a problem ____
A very big problem ____

10. Do you have a bed partner or roommate?

No bed partner or roommate ____
Partner/roommate in other room ____
Partner in same room, but not same bed ____
Partner in same bed ____

If you have a roommate or bed partner, ask him/her how often in the past month you have had_

(a) Loud snoring

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

(b) Long pauses between breaths while asleep

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

(c) Legs twitching or jerking while you sleep

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

(d) Episodes of disorientation or confusion during sleep

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

(e) Other restlessness while you sleep; please describe _____

_____

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

(j) Other reason(s), please describe _____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

6. During the past month, how would you rate your sleep quality overall?

Very good ____
Fairly good ____
Fairly bad ____
Very bad ____

7. During the past month, how often have you taken medicine (prescribed or "over the counter") to h you sleep?

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

8. During the past month, how often have you had trouble staying awake while driving, eating meals engaging in social activity?

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm get things done?

No problem at all ____
Only a very slight problem ____
Somewhat of a problem ____
A very big problem ____

10. Do you have a bed partner or roommate?

No bed partner or roommate ____
Partner/roommate in other room ____
Partner in same room, but not same bed ____
Partner in same bed ____

If you have a roommate or bed partner, ask him/her how often in the past month you have had_

(a) Loud snoring

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

(b) Long pauses between breaths while asleep

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

(c) Legs twitching or jerking while you sleep

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

(d) Episodes of disorientation or confusion during sleep

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

(e) Other restlessness while you sleep; please describe _____

_____

Not during the past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

APPENDIX D

NAME: **CODE:**

DATE	TIME	TYPE OF ACTIVITY	DURATION (MINS)	PACE	HOW YOU FELT

PTO

INSTRUCTIONS

ACTIVITY: walking, jogging, swimming, cycling, running on the spot, stair-stepping, dancing or other

DURATION: total time of continuous activity
list any stretching/warm-up/cool-down activity separately

PACE: slow, fast, moderate, faster/slower than normal
this is just to give me and you some idea of how your exercise capacity varies from day to day, ie. some days you may feel that you can push yourself a little harder, others you may feel exhausted and just manage a very gentle pace. Both are fine and it is important that you record it.

HOW YOU FELT: this is tied in with the pace you can manage on different days
record whether you feel tired, lively, stressed, weak,energetic etc.

APPENDIX E

Variable	Baseline (n=33)	Post flexibility treatment (n=30)	Significance	Post exercise treatment (n=23)	Significance vs post flexibility
VO_2 peak ($ml.kg^{-1}.min^{-1}$)	28.2 (23.4-33.1)	29.2 (25-35)	ns	31.5 (27.2-35.9)	0.000
VO_2 max ($l.min^{-1}$)	1.9 (1.4-2.4)	1.9 (1.6-2.2)	ns	2.1 (1.8-2.4)	0.000
Ventilation max ($l.min^{-1}$)	71.2 (52.6-89.7)	76.1 (64-88)	0.009	79.1 (66.3-92.0)	ns
Heart Rate max (BPM)	171 (19)	178 (14)	0.008	179 (12)	ns
Recovery Heart Rate (BPM)	111 (17)	115 (15)	ns	110 (11)	ns
Test Duration(minutes)	9.5 (3.6)	11.0 (3.3)	0.000	11.4 (3.0)	ns
Blood Lactate at RPE 14 ($mmol.l^{-1}$)	2.3 (1.4-3.4)	2.5 (1.6-3.4)	0.006	2.2 (1.5-3.0)	ns
Blood Lactate post test ($mmol.l^{-1}$)	5.8 (2.5)	6.2 (2.5)	0.02	6.3 (1.8)	ns
Total RPE	64 (21)	59 (20)	0.001	58 (20)	ns
FVC ($l.min^{-1}$)	3.2 (0.6)	3.2 (0.6)	ns	3.1 (0.6)	ns
FEV1 ($l.min^{-1}$)	3.9 (0.7)	3.9 (0.7)	ns	3.8 (0.8)	ns
FEV1/FVC Ratio	83 (5)	82 (4)	ns	81 (5.7)	ns
MVC (Newtons)	340 (105)	378 (106)	0.001	412 (152)	ns

Table 23. Physiological variables in flexibility group after 12 weeks of flexibility and relaxation followed by 12 weeks of aerobic exercise. Values are mean (SD) or median (IQR)

Variable	Baseline (n=33)	Post flexibility treatment (n=30)	Significance	Post exercise treatment (n=23)	Significance vs post flexibility
V/A Total Fatigue	324.6 (45.0)	286.0 (67.1)	0.03	277.0 (60.0)	ns
V/A Physical Fatigue	176.5 (16.4)	153.7 (34.0)	0.009	148.8 (29.1)	ns
V/A Mental Fatigue	148.1 (34.3)	132.1 (39.3)	ns	128.2 (40.3)	ns
Wessely fatigue	30.5 (5.6)	27.4 (7.4)	0.02	24.5 (7.4)	0.02
SF36 total score	336 (73)	420 (120)	0.05	448 (170)	ns
SF36-physical function	46 (18)	55 (21)	ns	62 (19)	0.02
SF36-role physical	0 (0-25)	0 (0-25)	ns	0 (0-75)	ns
SF36-bodily pain	41 (30-52)	54 (25)	ns	56 (28)	ns
SF36-general health	37 (16)	40 (25-55)	ns	48 (20)	0.05
SF36-vitality	22 (17-28)	40 (25-55)	0.01	40 (27-52)	ns
SF36-social function	38 (24)	56 (24)	0.04	55 (27)	ns
SF36-role emotional	84 (50-117)	100 (67-34)	ns	100 (75-125)	ns
SF36-mental health	64 (60-68)	76 (64-88)	0.03	68 (53-83)	ns
HAD depression	5.0 (2.5-7.5)	4 (0.6-7.4)	ns	5.4 (2.9)	ns
HAD anxiety	5.7 (4.0)	7.0 (3.5-10.5)	ns	7.0 (4.8-8-9.3)	ns
PSQI total score	6.5 (3.5)	6.0 (4.1-7.9)	ns	5.7 (2.8)	ns
Barskey amplification	9.7 (3.6)	8.5 (4.1)	0.04	7.0 (3.3-10.8)	ns

Table 24 Symptomatic variables in flexibility group after 12 weeks of flexibility and relaxation followed by 12 weeks of aerobic exercise. Values are mean (SD) or median (IQR)

APPENDIX F

Explanation of coding for psychological raw data

1 = baseline assessment
2 = retest 1
3 = retest 2 (F group) of 3 month follow up E group
4 = 3 month follow up F group

999	missing data
hada	HAD anxiety
hadd	HAD depression
pmf	persistent mental fatigue
ppf	persistent physical fatigue
epf	exertional physical fatigue
emf	exertional mental fatigue
wessely	Wessely total fatigue score
wesp	Wessely physical fatigue
wesm	Wessely mental fatigue
psqia	Pittsburgh sleep total score
psqib	Pittsburgh sleep duration
psqi6	Pittsburgh sleep latency
hsq	Health Status questionnaire
hsqpf	physical function
hsqrp	role physical
hsqbp	bodily pain
hsqgh	general health
hsqvi	vitality
hsqsf	social function
hsqre	role emotional
hsqmh	mental health
barskey	Barskey somatic amplification total score

Newdata

	code	group	basegrps	sex	retest	illdur	med	cause	age	height
1	1	1	5	2	1	5.0	0	0	38	174.0
2	4	1	5	1	5	4.0	1	11	28	178.0
3	10	1	5	1	1	3.5	1	11	23	171.5
4	12	1	5	2	1	2.0	0	1	34	169.5
5	13	1	5	1	1	4.0	0	1	22	179.0
6	15	1	5	2	1	4.5	2	1	47	169.0
7	19	1	5	2	1	3.8	0	0	57	169.5
8	14	1	5	2	1	.8	0	1	35	170.0
9	20	1	5	2	1	5.5	3	11	44	157.5
10	21	1	5	1	1	3.5	1	1	50	179.0
11	24	1	5	2	1	5.0	0	11	42	155.0
12	25	1	5	2	5	3.8	0	2	36	173.5
13	26	1	5	1	1	7.0	0	3	22	183.5
14	28	1	5	2	1	2.0	0	11	23	165.0
15	34	1	5	1	1	4.0	0	1	52	170.0
16	36	1	5	2	1	2.0	0	2	33	169.0
17	42	1	5	2	1	1.0	0	1	39	167.0
18	43	1	5	1	1	2.5	1	4	39	175.5
19	45	1	5	2	1	7.0	2	1	31	169.0
20	46	1	5	2	1	2.5	3	1	52	162.0
21	53	1	5	1	1	4.5	2	1	39	180.0
22	57	1	5	1	1	1.5	1	0	49	183.5
23	58	1	5	2	1	5.0	0	3	38	168.0
24	60	1	5	2	1	1.5	0	11	32	171.0
25	62	1	5	2	1	4.0	1	2	39	154.0
26	63	1	5	2	6	.8	2	1	29	161.0
27	64	1	5	2	1	11.0	0	0	45	165.0
28	65	1	5	2	1	17.0	2	0	44	170.0
29	66	1	5	2	1	3.0	0	11	28	166.0
30	50	1	5	2	6	2.0	0	0	38	162.0
31	23	1	5	1	6	1.5	1	1	48	171.5
32	35	1	5	2	6	4.0	0	0	31	158.5
33	16	1	5	2	1	4.5	1	2	43	176.0
34	2	2	5	2	4	5.0	0	1	46	160.5

Newdata

	weight	bmi	vo2maxm	vo2maxl	hrmax	vemax	hrrec	perhr	testd	rpe	lac14
1	67.2	22.2	34.5	2.32	166	100.0	106	90	12.0	75	3.6
2	84.4	26.6	43.4	3.66	176	111.9	114	93	14.0	89	9.9
3	62.8	21.2	36.7	2.88	179	104.1	126	92	12.0	89	3.0
4	61.1	21.4	31.7	1.94	153	75.4	86	81	12.0	71	1.4
5	83.8	26.2	37.9	3.17	190	94.7	120	99	14.0	92	4.6
6	61.4	21.5	38.4	2.36	170	94.5	120	94	12.0	76	3.9
7	61.5	21.5	32.0	1.97	183	80.2	90	106	10.0	77	1.6
8	65.7	22.7	35.8	1.69	189	71.8	115	101	10.0	67	3.0
9	54.9	22.0	36.5	2.00	151	64.6	113	83	8.0	64	1.3
10	82.7	25.8	33.3	2.76	162	136.8	120	91	6.5	58	5.3
11	61.5	25.6	27.8	1.71	163	59.6	94	89	8.0	60	1.4
12	59.5	18.9	29.9	1.78	166	61.5	88	89	12.0	69	1.6
13	69.0	20.4	44.9	3.10	206	121.0	129	105	18.0	118	4.2
14	58.7	21.5	37.7	2.22	207	89.7	147	106	13.5	109	2.0
15	85.0	29.0	31.1	2.47	149	65.8	88	85	11.0	66	2.8
16	58.6	20.5	29.4	1.72	185	66.6	108	98	10.0	72	2.7
17	82.6	29.3	20.8	1.72	128	71.3	70	69	4.5	53	2.0
18	71.2	23.0	40.0	2.85	182	125.8	119	98	14.5	84	4.0
19	78.0	27.3	18.8	1.47	171	73.6	139	90	8.5	58	4.1
20	50.0	19.0	24.8	1.24	136	52.4	91	77	5.5	45	1.9
21	102.0	31.1	30.7	3.12	167	120.0	112	89	11.0	87	4.3
22	86.9	25.7	44.5	3.87	170	130.9	100	96	20.0	106	4.3
23	61.9	21.9	27.3	1.66	162	66.2	119	85	10.0	67	3.5
24	68.6	25.5	25.6	1.73	165	59.7	106	87	10.0	74	1.6
25	56.3	23.7	22.0	1.24	156	45.6	94	84	7.5	62	3.7
26	48.1	18.6	27.7	1.33	164	56.9	103	86	10.5	68	2.1
27	57.0	20.9	38.4	2.16	183	63.8	110	101	16.0	118	1.0
28	54.8	19.0	18.3	1.00	154	41.3	74	85	7.0	65	2.5
29	55.4	20.1	28.4	1.57	185	65.3	116	94	12.0	80	2.8
30	52.1	19.9	35.1	1.82	178	71.0	113	95	11.5	78	2.4
31	95.4	32.2	18.8	1.79	159	60.1	118	89	2.5	14	1.7
32	50.6	20.0	31.9	1.61	184	61.6	131	97	8.0	55	.5
33	136.4	43.7	99.9	9.99	177	999.9	108	97	6.0	55	4.8
34	48.0	18.8	30.6	1.47	161	63.2	95	89	12.0	84	4.1

Newdata

	lac14b	postlac	isostr	fev1	fvc1	ratio1	skf	hada1	hadd1	pmf1	ppf1
1	9.9	7.8	263	9.9	9.9	99	999.9	5	5	76	74
2	9.9	99.9	696	9.9	9.9	99	999.9	3	6	999	999
3	9.9	8.3	468	9.9	9.9	99	25.5	13	3	999	999
4	9.9	1.8	253	2.7	4.4	61	999.9	8	11	77	87
5	9.9	6.7	663	4.0	5.4	73	99.9	3	4	88	93
6	9.9	6.7	383	3.0	4.1	73	99.9	3	2	80	65
7	9.9	6.5	273	9.9	9.9	99	47.2	5	2	31	55
8	9.9	7.2	308	3.2	4.1	77	68.5	1	2	57	65
9	9.9	4.8	273	2.8	3.6	78	48.3	6	12	79	100
10	9.9	6.9	427	3.6	4.8	73	999.9	8	5	57	57
11	9.9	4.8	149	2.2	3.7	60	67.6	12	10	85	74
12	9.9	3.3	235	2.9	4.1	70	37.1	4	9	66	71
13	9.9	6.3	433	9.9	9.9	99	42.8	7	2	48	40
14	9.9	5.2	331	9.9	9.9	99	29.9	6	9	82	92
15	9.9	5.0	489	2.2	3.6	62	999.9	3	5	67	81
16	9.9	3.7	352	2.3	3.1	75	44.6	3	9	100	100
17	9.9	4.3	239	2.2	3.4	64	92.0	4	10	88	90
18	9.9	8.9	447	4.1	4.7	88	49.7	8	11	79	94
19	9.9	7.4	304	9.9	9.9	99	100.8	2	3	85	85
20	9.9	2.9	165	2.1	2.6	81	30.3	7	5	76	82
21	9.9	3.3	575	4.6	5.5	83	83.1	9	2	66	64
22	9.9	8.3	588	4.3	5.2	82	45.4	12	19	72	72
23	9.9	5.2	128	1.9	2.9	64	54.5	4	2	66	76
24	9.9	2.9	246	3.5	4.2	81	53.1	8	1	68	63
25	9.9	4.0	290	2.3	2.6	88	63.6	12	7	100	100
26	9.9	3.7	401	2.9	3.2	91	34.8	99	99	999	999
27	9.9	2.6	247	3.6	4.2	87	36.4	5	5	76	63
28	9.9	5.8	164	2.9	3.5	83	52.2	1	5	72	82
29	9.9	6.1	248	3.5	3.9	89	55.5	6	2	62	85
30	9.9	4.9	290	2.7	3.3	82	47.6	12	2	50	75
31	9.9	1.7	170	3.4	4.3	79	999.9	4	9	72	79
32	9.9	4.2	354	2.7	3.2	83	35.5	0	3	68	87
33	9.9	7.4	348	2.4	3.3	74	999.9	1	5	70	97
34	9.9	7.2	268	9.9	9.9	99	999.9	14	6	999	999

Newdata

	epf1	emf1	wessely1	wesp1	wesm1	psqia1	psqib1	psqi61	hsqpf1	hsqrp1
1	73	69	31	20	11	8	0	0	999	999
2	999	999	20	12	8	4	0	0	999	999
3	999	999	10	7	3	7	1	0	999	999
4	88	77	33	14	19	9	1	1	999	999
5	100	100	30	18	12	12	1	1	999	999
6	87	91	32	22	10	5	0	0	999	999
7	65	65	32	19	13	10	0	0	95	0
8	62	54	18	12	6	99	9	0	999	999
9	100	82	34	21	13	7	1	1	999	999
10	62	63	25	14	11	9	1	1	999	999
11	74	93	33	20	13	8	0	0	40	0
12	53	79	37	20	17	3	1	1	55	0
13	61	52	11	5	6	8	0	1	75	75
14	97	91	37	20	17	6	1	1	30	0
15	59	54	21	15	6	8	0	0	85	25
16	100	100	36	23	13	5	1	0	35	0
17	94	94	35	21	14	8	1	0	15	0
18	69	57	33	21	12	5	0	0	45	0
19	84	84	38	21	17	7	1	0	45	0
20	89	87	30	18	12	3	0	0	40	0
21	70	73	28	14	14	8	0	0	50	0
22	84	83	35	24	11	7	0	1	70	0
23	92	90	25	16	9	4	0	0	40	25
24	86	68	24	17	7	5	0	0	70	50
25	100	100	34	22	10	99	9	9	999	999
26	999	999	99	.	.	99	9	9	999	999
27	74	76	28	17	11	99	0	9	999	999
28	86	86	25	17	11	5	0	0	35	50
29	96	83	28	19	9	5	1	0	45	0
30	93	94	22	15	6	4	0	1	55	0
31	95	85	32	19	13	6	0	0	40	0
32	94	72	29	19	10	1	1	0	5	0
33	97	66	31	20	11	9	1	0	999	999
34	999	999	28	16	12	7	1	0	999	999

Newdata

	hsqbp1	hsqgh1	hsqvi1	hsqsc1	hsqre	hsqme1	baskey1	skida1	skidb1	age2
1	999	999	999	999	999	999	20	0	0	38
2	999	999	999	999	999	999	7	0	0	28
3	999	999	999	999	999	999	8	0	0	23
4	999	999	999	999	999	999	6	0	0	34
5	999	999	999	999	999	999	4	0	0	22
6	999	999	999	999	999	999	6	0	0	47
7	90	57	60	12	38	33	12	0	0	57
8	999	999	999	999	999	999	99	0	0	35
9	999	999	999	999	999	999	12	0	0	44
10	999	999	999	999	999	999	10	0	0	50
11	42	47	40	67	0	40	13	9	0	42
12	41	25	35	40	100	68	13	9	0	36
13	84	50	0	75	100	70	3	0	0	22
14	90	45	5	0	33	72	2	9	0	23
15	74	37	35	88	0	56	6	99	99	52
16	41	35	50	50	0	64	5	0	0	34
17	12	45	30	0	33	72	10	9	0	40
18	52	20	15	25	0	36	13	9	0	39
19	31	50	20	38	100	92	9	0	0	31
20	52	50	40	38	100	76	7	0	0	52
21	41	45	40	50	66	76	9	0	0	39
22	25	25	25	13	0	44	9	0	0	49
23	31	62	20	38	100	72	9	6	0	38
24	32	45	45	63	33	64	10	0	0	32
25	999	999	999	999	999	999	13	9	0	39
26	999	999	999	999	999	999	99	0	0	99
27	999	999	999	999	999	999	6	0	0	45
28	50	20	10	88	100	60	4	0	0	44
29	31	15	45	75	100	76	11	0	0	28
30	51	52	55	63	33	64	12	0	0	99
31	31	40	45	13	100	72	11	0	0	99
32	21	15	40	13	100	88	9	0	0	99
33	999	999	999	999	999	999	8	0	0	43
34	999	999	999	999	999	999	13	0	0	46

Newdata

	height2	weight2	vo2maxm2	vo2maxl2	vemax2	hrmax2	perhrm2	hrrec2	testd2
1	174.0	64.2	36.5	2.38	95.0	170	92	116	14.0
2	178.0	80.4	45.0	3.62	156.4	186	97	135	16.0
3	171.5	63.1	47.2	2.98	118.4	187	96	131	14.0
4	169.5	61.5	36.2	2.20	69.4	154	82	86	10.0
5	179.0	83.7	41.3	3.46	107.7	192	98	119	14.0
6	169.0	60.8	38.1	2.31	104.9	173	96	118	15.5
7	169.5	62.0	39.2	2.43	97.9	186	107	104	10.0
8	170.0	65.2	32.8	2.11	81.5	187	100	115	10.5
9	157.5	54.9	36.6	2.01	94.1	176	97	115	12.5
10	179.0	84.6	35.3	2.99	137.6	165	93	118	12.5
11	155.0	59.6	34.1	2.03	68.1	154	84	94	10.0
12	173.5	57.3	38.2	2.20	67.8	166	89	86	12.0
13	183.5	65.7	49.7	3.26	113.2	194	101	123	20.0
14	165.0	57.5	43.7	2.51	100.2	199	102	133	15.0
15	170.0	84.8	30.5	2.59	63.6	139	79	68	12.0
16	169.0	58.7	31.8	1.86	73.6	186	101	118	12.0
17	167.0	88.9	21.2	1.89	85.6	142	77	63	6.0
18	175.5	72.9	44.8	3.14	146.8	180	97	105	16.0
19	169.0	80.5	27.0	2.17	91.5	172	90	141	10.0
20	162.5	50.0	30.5	1.52	56.3	144	82	95	7.5
21	180.0	103.0	39.6	4.08	125.2	167	90	132	16.5
22	183.5	92.3	40.1	3.62	122.3	171	96	102	18.5
23	167.5	61.9	27.6	1.71	75.5	160	86	98	10.5
24	171.0	68.4	23.4	1.60	75.6	174	92	109	12.0
25	154.0	57.7	23.1	1.34	50.3	165	89	114	10.0
26	999.9	999.9	99.9	9.99	999.9	999	.	999	99.9
27	165.0	58.5	33.7	1.97	66.8	160	88	90	17.0
28	170.5	55.7	22.6	1.26	58.3	167	92	89	9.5
29	166.0	55.5	30.0	1.66	75.5	179	93	105	12.0
30	999.9	999.9	99.9	9.99	999.9	999	.	999	99.9
31	999.9	999.9	99.9	9.99	999.9	999	.	999	99.9
32	999.9	999.9	99.9	9.99	999.9	999	.	999	99.9
33	176.0	135.7	99.9	9.99	999.9	174	96	113	6.0
34	160.5	47.8	30.2	1.38	57.5	161	95	84	14.0

Newdata

	rpe2	lac142	lac14b2	postlac2	isostr2	fev12	fvc2	ratio2	skf2	hada2
1	69	3.6	3.4	4.6	252	9.9	9.9	99	999.9	5
2	67	4.6	9.8	10.8	560	9.9	9.9	99	999.9	7
3	72	2.7	3.3	8.9	675	4.8	5.4	89	26.4	5
4	67	1.3	9.9	2.0	321	3.7	4.4	83	999.9	7
5	90	3.6	9.9	7.7	1019	3.9	5.2	74	73.4	6
6	76	3.0	9.9	9.1	412	3.0	3.8	77	999.9	3
7	61	1.4	2.8	6.2	346	2.0	3.4	59	49.0	7
8	68	3.9	3.7	9.1	387	3.2	4.1	77	65.9	0
9	48	1.0	2.2	5.8	468	2.8	3.7	76	999.9	5
10	45	2.0	4.0	7.3	562	9.9	9.9	99	41.2	9
11	55	2.0	2.2	5.4	364	2.4	3.6	67	71.6	99
12	62	1.4	9.9	2.9	235	3.0	4.2	71	34.1	99
13	91	2.0	3.4	5.4	526	4.2	5.4	76	30.2	10
14	86	1.8	2.2	4.9	362	2.7	2.7	97	31.2	99
15	69	1.2	1.2	2.6	694	2.4	3.7	64	999.9	2
16	68	1.9	1.9	4.5	479	2.3	3.2	74	999.9	4
17	47	1.7	9.9	6.5	199	3.1	3.9	78	100.0	2
18	79	3.2	9.9	10.8	607	4.3	5.1	85	48.6	6
19	52	2.5	3.5	8.1	389	3.0	3.3	91	999.9	2
20	41	1.1	1.7	2.6	233	2.4	3.1	77	27.1	3
21	77	1.5	1.5	7.1	525	4.6	5.5	83	97.0	8
22	116	4.2	9.9	7.7	555	4.1	5.0	82	45.5	8
23	57	2.8	9.9	6.8	431	2.1	3.3	63	53.2	8
24	68	1.9	4.9	4.8	298	3.5	4.2	81	67.2	7
25	46	2.9	2.9	5.6	284	2.3	2.5	88	70.5	8
26	999	9.9	9.9	99.9	9999	9.9	9.9	99	999.9	99
27	98	1.1	2.0	2.7	290	3.3	4.0	84	38.0	5
28	51	2.8	4.0	9.8	197	3.1	3.7	85	53.6	1
29	67	2.5	9.9	4.9	259	3.4	4.0	88	53.8	8
30	999	9.9	9.9	99.9	9999	9.9	9.9	99	999.9	3
31	999	9.9	9.9	99.9	9999	9.9	9.9	99	999.9	99
32	999	9.9	9.9	99.9	9999	9.9	9.9	99	999.9	99
33	47	4.0	9.9	5.6	537	2.2	3.0	72	999.9	4
34	83	2.6	9.9	4.6	319	3.0	3.7	80	34.3	5

Newdata

	hadd2	pmf2	ppf2	epf2	emf2	wessely	wesp2	wesm2	psqia2	psqib2	psqi6
1	5	999	999	999	999	33	20	13	6	0	0
2	3	50	50	50	50	11	3	8	7	1	1
3	1	32	54	43	40	6	3	3	4	0	0
4	10	75	75	91	75	28	14	14	10	1	1
5	6	89	82	91	100	34	13	21	13	1	1
6	1	56	45	45	87	20	15	5	5	0	0
7	6	73	62	59	59	3	0	3	5	0	0
8	1	54	70	66	52	22	15	7	1	0	0
9	7	91	75	50	94	19	12	7	5	1	0
10	8	54	53	53	64	28	16	12	7	1	0
11	99	999	999	999	999	99	7	6	99	9	9
12	99	999	999	999	999	99	.	.	99	9	9
13	7	33	36	52	50	11	5	6	6	1	0
14	99	999	999	999	999	99	14	4	99	9	9
15	9	69	83	90	70	28	17	11	5	1	0
16	11	72	72	57	64	28	17	11	2	0	0
17	3	62	59	81	55	14	6	8	4	0	0
18	7	63	66	61	65	27	16	11	5	0	0
19	1	67	66	86	69	31	18	13	6	0	0
20	4	63	77	88	83	22	13	9	4	0	0
21	6	55	67	67	59	24	14	10	8	0	0
22	9	67	66	79	63	33	23	10	5	0	0
23	4	75	73	87	74	6	2	4	4	0	0
24	6	57	60	81	59	20	14	6	4	0	0
25	10	50	50	50	50	7	3	4	7	0	0
26	99	999	999	999	999	99	.	.	99	9	9
27	1	54	56	43	62	22	14	8	1	0	0
28	2	52	52	58	61	31	21	10	5	0	0
29	2	53	45	53	72	17	10	7	8	0	1
30	2	65	61	63	67	21	16	6	5	0	0
31	99	999	999	999	999	99	.	.	99	9	9
32	99	999	999	999	999	99	.	.	99	9	9
33	5	27	84	86	15	20	15	5	11	1	0
34	5	999	999	999	999	99	.	.	4	0	0

Newdata

	hsqpf2	hsqrf2	hsqbp2	hsqgh2	hsqvi2	hsqsf2	hsqre2	hsqmh2	baskey2	skida2
1	999	999	999	999	999	999	999	999	99	0
2	999	999	999	999	999	999	999	999	13	0
3	100	75	62	77	50	63	100	84	10	0
4	55	0	31	72	35	7	1	3	3	0
5	65	0	51	40	25	13	33	20	10	0
6	95	25	74	55	45	75	100	80	6	0
7	80	25	72	85	70	88	67	84	10	0
8	85	0	84	35	50	38	100	88	9	0
9	75	75	72	67	40	63	100	64	10	0
10	85	25	75	35	45	75	33	44	14	0
11	999	999	999	999	999	999	999	999	99	99
12	999	999	999	999	999	999	999	999	99	99
13	100	100	100	75	75	100	100	64	9	0
14	70	50	54	40	30	63	100	84	99	0
15	90	25	84	40	25	100	67	60	8	14
16	75	25	90	45	20	63	67	64	9	99
17	50	0	41	60	45	100	100	84	17	99
18	60	25	90	40	40	75	100	76	9	99
19	70	25	41	40	40	38	100	88	2	0
20	30	0	51	65	35	38	67	68	6	0
21	55	0	41	45	65	50	100	44	7	0
22	80	0	84	30	40	38	0	36	3	9
23	50	75	62	50	40	50	100	80	7	0
24	75	75	62	35	40	88	100	76	10	0
25	50	100	74	47	75	100	100	88	11	9
26	999	999	999	999	999	999	999	999	99	0
27	80	50	50	77	50	63	100	80	5	0
28	55	50	50	30	40	88	100	84	6	0
29	65	25	31	35	55	63	100	68	6	0
30	60	0	90	50	40	88	100	76	13	0
31	999	999	999	999	999	999	999	999	99	99
32	999	999	999	999	999	999	999	999	99	99
33	40	25	62	72	30	75	100	88	9	9
34	999	999	999	999	999	999	999	999	99	0

Newdata

	skidb2	cgio2	cgid2	cgip2	cgi2full	age3	height3	weight3	vo2maxm3
1	0	9	9	2	4	39	174.0	67.8	36.2
2	0	9	1	1	1	99	999.9	999.9	99.9
3	0	1	1	1	1	23	171.5	63.5	53.9
4	0	1	2	2	3	34	169.5	61.9	27.9
5	0	9	1	1	2	23	179.0	82.1	46.9
6	0	2	2	2	3	47	169.0	61.0	38.2
7	0	1	1	1	1	58	169.5	64.4	31.9
8	0	9	1	1	3	35	170.0	65.4	28.5
9	0	9	1	1	2	44	157.5	53.7	37.7
10	0	1	1	1	1	50	179.0	85.6	36.6
11	99	9	1	1	2	42	156.0	62.0	29.8
12	99	9	9	2	4	99	999.9	999.9	99.9
13	0	1	1	1	1	23	184.0	65.5	47.7
14	0	1	2	2	3	24	166.0	60.4	38.4
15	0	2	2	2	5	52	170.0	85.5	33.0
16	99	3	2	2	3	34	169.0	59.0	35.7
17	99	9	1	1	2	40	167.0	92.0	21.8
18	99	9	1	1	2	39	175.5	73.4	42.8
19	0	3	2	2	3	31	169.0	81.0	30.0
20	0	3	1	2	3	52	162.5	50.1	17.2
21	0	9	1	1	1	39	180.0	101.2	40.9
22	0	3	2	2	3	49	183.5	92.8	40.3
23	0	2	1	1	2	38	168.0	62.6	24.5
24	0	3	2	2	3	32	171.0	67.1	28.1
25	0	2	1	1	1	40	154.0	52.2	28.3
26	0	3	2	2	9	29	999.9	999.9	99.9
27	0	3	2	2	3	45	165.0	57.4	34.2
28	0	4	2	2	3	45	171.0	54.8	23.3
29	0	3	1	1	3	29	65.0	56.0	30.0
30	0	9	1	1	9	99	999.9	999.9	99.9
31	99	9	9	9	9	99	999.9	999.9	99.9
32	99	9	9	9	9	99	999.9	999.9	99.9
33	0	1	1	1	1	43	176.0	139.2	99.9
34	0	9	2	2	3	46	160.5	47.6	36.5

	vo2maxl3	vemax3	hrmax3	hrrec3	testd3	rpe3	lac143	lac14b3	postlac3
1	2.45	97.0	174	117	13.5	76	2.8	5.7	5.9
2	9.99	999.9	999	999	99.9	99	9.9	9.9	99.9
3	3.38	146.4	197	140	16.0	62	4.5	4.8	11.2
4	1.72	57.0	142	82	10.0	63	1.5	1.5	1.7
5	3.85	122.2	205	130	18.0	80	1.8	3.4	9.0
6	2.31	92.9	172	112	12.0	79	2.1	2.3	8.4
7	2.06	89.1	185	96	13.5	52	2.8	3.0	5.5
8	1.87	77.0	186	124	10.0	69	2.0	3.9	7.3
9	2.02	85.2	179	115	12.5	52	2.6	3.5	7.6
10	3.13	140.6	164	119	13.0	41	2.7	5.8	7.8
11	1.85	60.9	156	88	10.0	52	2.5	3.5	9.9
12	9.99	999.9	999	999	99.9	999	9.9	9.9	99.9
13	3.12	117.4	199	127	19.0	82	2.6	6.9	7.6
14	2.35	90.8	208	130	14.0	98	2.2	3.2	6.0
15	2.83	73.7	162	88	12.5	64	9.9	4.2	7.4
16	2.11	87.5	194	118	14.0	67	3.4	6.7	7.0
17	2.01	97.5	143	70	6.0	41	2.0	2.5	8.1
18	3.14	163.4	184	118	17.0	70	7.9	7.8	11.3
19	2.45	85.9	170	141	10.5	47	2.4	3.0	5.4
20	.87	34.6	115	74	4.0	30	1.2	9.9	1.2
21	4.14	137.2	164	113	17.0	75	2.2	1.9	6.4
22	3.74	125.9	171	97	18.5	120	2.4	3.8	9.5
23	1.53	67.6	161	101	9.0	60	3.2	3.8	4.9
24	1.88	78.8	188	127	12.0	68	2.0	9.9	5.3
25	1.48	58.5	185	107	10.0	52	3.2	9.9	4.7
26	9.99	999.9	999	999	99.9	999	9.9	9.9	99.9
27	1.96	71.3	172	101	17.0	87	2.0	2.9	4.3
28	1.28	57.9	168	83	9.5	53	2.6	3.2	6.3
29	1.68	70.0	176	93	12.0	78	.9	9.9	9.9
30	9.99	999.9	999	999	99.9	999	9.9	9.9	99.9
31	9.99	999.9	999	999	99.9	999	9.9	9.9	99.9
32	9.99	999.9	999	999	99.9	999	9.9	9.9	99.9
33	9.99	999.9	178	103	6.0	43	5.6	9.9	7.3
34	1.74	67.2	168	90	13.5	77	3.0	5.2	6.8

Newdata

	isostr3	fev13	fvc3	ratio	skf3	hada3	hadd3	pmf3	ppf3	epf3	emf3
1	262	9.9	9.9	99	999.9	8	2	24	26	27	31
2	9999	9.9	9.9	99	999.9	99	99	999	999	999	999
3	960	4.7	5.5	84	20.5	99	99	999	999	999	999
4	494	4.1	4.7	86	999.9	6	8	50	76	80	50
5	792	3.8	5.1	74	74.0	99	99	999	999	999	999
6	388	3.0	4.0	75	999.9	5	1	76	67	52	99
7	429	2.7	3.4	80	50.2	4	1	54	61	67	57
8	360	3.4	4.2	80	62.6	0	2	56	71	68	53
9	593	2.8	3.7	76	45.0	8	6	45	50	54	50
10	644	4.0	5.3	75	39.7	11	8	49	52	52	52
11	299	2.7	3.5	76	70.8	9	9	75	78	90	91
12	9999	9.9	9.9	99	999.9	99	99	999	999	999	999
13	585	4.1	5.1	80	20.5	10	1	27	31	61	57
14	540	3.3	4.2	79	32.4	4	3	71	65	58	57
15	622	2.2	3.8	61	999.9	1	6	55	89	97	53
16	429	2.2	2.6	84	53.0	4	8	75	77	75	76
17	256	3.2	4.0	81	107.0	6	8	79	87	53	59
18	537	4.4	5.2	85	51.5	10	10	71	69	66	65
19	485	2.9	3.5	83	103.6	0	2	64	65	67	65
20	294	2.3	3.1	76	31.0	5	7	85	86	92	92
21	612	4.5	5.3	85	72.0	5	3	74	71	72	68
22	538	3.9	4.7	82	48.5	8	8	61	83	94	89
23	417	1.9	3.2	60	55.8	7	12	54	50	68	42
24	358	3.4	4.2	81	63.4	6	5	51	66	61	53
25	9999	2.2	2.5	88	59.0	6	1	72	71	99	70
26	9999	9.9	9.9	99	999.9	99	99	999	999	999	999
27	301	3.6	4.0	90	37.4	13	8	77	50	50	76
28	187	3.0	3.6	83	52.5	3	2	64	68	70	67
29	272	3.6	3.9	91	48.0	4	1	49	54	60	42
30	9999	9.9	9.9	99	999.9	13	7	79	90	95	80
31	9999	9.9	9.9	99	999.9	99	99	999	999	999	999
32	9999	9.9	9.9	99	999.9	99	99	999	999	999	999
33	465	2.4	3.3	74	999.9	4	2	60	75	68	57
34	391	3.1	3.9	78	33.8	3	4	55	55	53	55

Newdata

	wessely3	wesp3	wesm3	psqia3	psqib3	psqi63	hsqpf3	hsqrp3	hsqbp	hsqgh3
1	20	.	.	8	0	0	65	0	52	30
2	99	.	.	99	9	9	999	999	999	999
3	99	.	.	99	9	9	95	50	72	77
4	32	.	.	12	1	1	50	25	31	50
5	99	.	.	99	9	9	70	0	51	65
6	4	.	.	5	0	0	90	25	72	35
7	24	.	.	9	1	0	70	0	41	77
8	22	.	.	1	0	0	80	0	84	35
9	25	.	.	4	1	0	80	50	84	62
10	26	.	.	7	1	0	90	25	42	47
11	12	.	.	10	0	0	45	0	41	35
12	99	.	.	99	9	9	999	999	999	999
13	13	.	.	4	0	0	95	100	90	92
14	28	.	.	7	0	0	70	50	84	52
15	21	.	.	10	1	1	85	50	74	47
16	24	.	.	4	0	0	75	25	90	45
17	15	.	.	9	1	0	70	0	52	65
18	29	.	.	6	1	0	60	50	74	60
19	27	.	.	6	0	0	75	25	62	55
20	21	.	.	4	0	0	55	0	62	55
21	26	.	.	12	1	1	40	25	51	30
22	35	.	.	7	0	0	60	0	84	35
23	4	.	.	5	0	0	70	25	74	57
24	19	.	.	5	0	0	80	100	44	30
25	16	.	.	11	2	1	50	0	31	25
26	99	.	.	99	9	9	999	999	999	999
27	24	.	.	7	0	0	85	50	50	77
28	23	.	.	4	0	2	26	0	41	75
29	23	15	8	5	0	1	80	0	44	40
30	35	.	.	3	0	0	60	0	62	40
31	99	.	.	9	9	9	999	999	999	999
32	99	.	.	9	9	9	999	999	999	999
33	18	.	.	5	1	0	35	0	62	67
34	25	16	9	5	1	0	75	75	84	40

Newdata

	hsqvi3	hsqsf3	hsqre3	hsqmh3	baskey3	skida3	skidb3	cgio3	cgid3	cgip3
1	0	38	0	52	20	5	0	9	4	4
2	999	999	999	999	99	99	99	9	9	9
3	55	75	100	80	99	0	0	1	1	1
4	45	75	67	64	4	0	0	1	3	3
5	10	63	33	68	99	99	99	9	9	1
6	35	63	100	80	6	0	0	9	9	3
7	70	63	67	80	9	99	99	9	9	1
8	30	50	100	84	9	0	0	3	4	3
9	45	75	0	56	7	0	0	1	2	2
10	45	50	33	60	16	0	0	1	1	1
11	30	50	100	72	12	99	99	9	9	3
12	999	999	999	999	99	99	99	9	9	9
13	60	100	100	60	5	99	99	9	9	2
14	24	50	100	88	2	99	99	1	2	2
15	20	100	100	84	7	2	0	9	9	4
16	35	75	33	64	1	2	0	1	2	2
17	50	75	100	88	17	99	99	9	9	1
18	45	75	100	68	12	99	99	9	9	2
19	40	38	100	72	4	0	0	9	2	2
20	25	63	67	76	5	0	0	2	2	2
21	55	38	100	84	8	0	0	9	2	2
22	10	38	48	0	8	2	0	3	3	2
23	60	63	100	80	9	0	0	2	1	2
24	55	50	100	72	10	0	0	3	2	2
25	45	75	67	76	10	0	0	9	9	1
26	999	999	999	999	99	99	99	9	9	9
27	40	50	0	44	6	2	5	4	3	3
28	25	75	100	60	99	0	0	4	3	3
29	42	75	100	98	14	0	0	2	2	2
30	30	75	0	64	15	9	0	9	9	9
31	999	999	999	999	99	99	99	9	9	9
32	999	999	999	999	99	99	99	9	9	9
33	50	50	33	80	11	0	0	1	1	1
34	45	25	67	68	9	0	0	1	1	1

Newdata

	code	group	basegrps	sex	retest	illdur	med	cause	age	height
35	3	2	5	2	2	2.0	2	2	61	162.5
36	5	2	5	2	4	.6	0	2	32	165.5
37	7	2	5	2	4	1.0	0	2	29	170.5
38	8	2	5	1	4	1.5	0	1	64	176.0
39	9	2	5	2	3	3.0	0	1	24	160.0
40	11	2	5	2	4	.8	1	1	27	164.0
41	18	2	5	1	4	2.0	1	1	59	170.0
42	22	2	5	2	4	3.0	1	1	25	175.5
43	27	2	5	2	4	2.0	1	1	29	177.0
44	29	2	5	2	2	.6	0	1	46	170.5
45	31	2	5	2	2	19.0	0	11	35	169.0
46	32	2	5	2	2	1.3	2	1	40	163.0
47	30	2	5	2	2	7.0	0	1	21	170.0
48	33	2	5	2	4	5.0	1	4	24	161.0
49	37	2	5	2	4	.8	0	4	29	160.5
50	38	2	5	1	2	2.5	0	1	24	177.5
51	39	2	5	2	4	2.8	0	1	36	152.0
52	40	2	5	2	2	3.5	1	1	53	162.0
53	41	2	5	1	3	1.4	0	1	37	180.5
54	44	2	5	2	4	2.0	1	11	21	173.0
55	17	2	5	2	4	2.0	1	1	51	169.0
56	48	2	5	2	4	2.0	1	1	39	161.5
57	49	2	5	2	4	16.0	2	1	48	160.0
58	51	2	5	1	4	6.0	1	1	31	176.0
59	52	2	5	1	4	6.0	0	1	45	176.0
60	54	2	5	2	4	1.1	1	1	26	161.0
61	55	2	5	2	4	1.0	0	0	32	164.5
62	56	2	5	2	4	.8	2	1	47	176.0
63	59	2	5	2	4	1.0	0	1	24	179.5
64	61	2	5	2	6	.8	2	4	33	164.0
65	47	2	5	2	6	2.5	1	1	39	170.5
66	6	2	5	1	6	3.0	0	0	31	179.0

Newdata

	weight	bmi	vo2maxm	vo2maxl	hrmax	vemax	hrrec	perhr	testd	rpe	lac14
35	80.6	30.3	28.0	2.29	165	66.1	88	97	10.0	68	3.1
36	75.4	27.4	28.4	2.14	180	68.8	135	95	8.0	58	3.0
37	65.5	22.4	43.7	2.81	191	98.9	122	100	13.5	92	4.3
38	53.2	17.7	40.5	2.02	166	67.2	120	99	10.5	67	1.5
39	45.7	17.6	45.4	2.05	172	72.1	106	89	13.5	77	1.9
40	57.2	21.3	23.7	1.35	194	54.8	125	98	8.0	64	1.7
41	88.5	30.6	30.6	2.71	161	84.1	105	94	10.0	66	4.3
42	82.6	26.6	27.2	2.25	194	112.2	136	100	7.8	57	6.1
43	69.3	22.1	17.9	1.24	169	51.3	116	88	4.0	28	4.8
44	66.9	23.3	24.8	1.66	160	58.3	94	84	8.0	58	2.4
45	60.4	21.2	33.2	2.00	184	69.8	115	98	12.0	79	1.9
46	59.1	22.2	14.9	.88	115	37.5	64	59	4.0	34	1.0
47	51.9	17.9	34.7	1.80	182	72.7	121	93	12.0	84	3.4
48	61.7	23.8	31.0	1.91	162	61.7	105	87	8.0	64	2.1
49	67.8	26.1	25.0	1.70	182	56.2	104	95	8.0	54	4.2
50	56.5	17.8	36.5	2.10	188	69.7	139	97	10.0	69	3.5
51	63.5	27.4	26.1	1.66	171	50.1	106	93	12.0	73	1.0
52	84.3	32.1	22.4	1.88	143	72.4	80	81	4.5	25	9.9
53	79.8	24.4	27.0	2.15	149	74.0	105	80	6.5	39	4.2
54	52.9	17.6	29.7	1.58	185	57.9	107	94	10.0	63	4.5
55	74.8	26.8	22.8	1.65	169	77.8	111	97	6.0	52	4.1
56	64.6	24.6	24.9	1.61	177	61.8	107	96	8.8	53	2.4
57	65.4	25.5	28.4	1.86	176	61.0	112	98	8.8	55	2.0
58	79.4	25.6	47.9	3.56	187	152.5	118	98	16.0	94	3.9
59	72.0	23.2	49.5	3.56	184	131.5	127	100	18.0	119	2.1
60	50.4	19.4	28.8	1.45	186	85.9	149	96	12.0	61	1.7
61	79.0	29.0	26.8	2.11	151	67.3	106	80	8.0	63	1.3
62	88.0	28.7	16.6	1.44	128	74.0	84	70	4.0	35	9.9
63	79.2	24.4	23.8	1.89	195	75.9	109	100	11.0	75	1.4
64	56.7	21.1	14.5	.82	155	66.5	107	82	4.0	32	1.8
65	62.9	21.5	28.2	1.77	178	75.0	109	96	10.5	70	3.0
66	78.2	24.1	44.0	3.44	192	134.8	125	100	15.5	97	6.6

Newdata

	lac14b	postlac	isostr	fev1	fvc1	ratio1	skf	hada1	hadd1	pmf1	ppf1
35	9.9	8.0	301	9.9	9.9	99	999.9	4	7	999	999
36	9.9	3.9	235	9.9	9.9	99	999.9	8	7	999	999
37	9.9	7.8	396	9.9	9.9	99	999.9	7	1	999	999
38	9.9	2.6	311	9.9	9.9	99	999.9	3	2	100	100
39	9.9	3.9	399	9.9	9.9	99	999.9	11	3	85	89
40	9.9	5.6	376	3.3	4.0	82	45.8	3	4	46	81
41	9.9	4.5	617	2.7	3.1	86	74.7	1	1	61	89
42	9.9	8.7	349	2.3	2.8	80	104.2	10	8	100	100
43	9.9	4.8	423	9.9	9.9	99	87.6	99	99	67	92
44	9.9	3.2	338	9.9	9.9	99	57.1	3	2	65	62
45	9.9	4.9	339	3.6	4.3	84	45.7	9	7	89	89
46	9.9	1.6	153	9.9	9.9	99	48.7	0	3	53	95
47	9.9	4.8	279	3.7	4.5	81	35.4	4	5	44	82
48	9.9	3.6	298	3.0	3.9	77	67.2	8	10	84	88
49	9.9	5.4	326	9.9	9.9	99	86.4	1	9	70	76
50	9.9	6.1	414	3.8	4.2	91	23.1	10	9	69	68
51	9.9	2.7	259	2.1	2.4	87	57.6	12	6	95	96
52	9.9	99.9	209	2.8	3.0	79	84.6	2	10	88	90
53	9.9	2.1	310	3.6	4.1	88	52.1	6	7	91	91
54	9.9	7.8	286	3.3	3.6	89	28.7	1	5	94	95
55	9.9	9.8	274	2.5	3.2	79	87.8	3	8	69	92
56	9.9	7.2	228	3.2	3.8	84	71.4	11	10	80	90
57	9.9	4.6	280	2.3	3.1	75	72.8	3	2	58	83
58	9.9	9.2	491	4.2	5.0	83	50.0	10	5	85	87
59	9.9	9.6	545	3.6	4.7	76	42.5	9	8	76	90
60	9.9	5.8	486	2.9	3.1	94	35.5	4	2	50	73
61	9.9	3.2	347	3.2	3.8	84	89.7	1	3	67	76
62	9.9	2.9	355	3.8	4.5	84	96.0	0	5	64	73
63	9.9	3.5	278	3.9	4.9	81	57.6	7	5	61	90
64	9.9	3.6	175	3.6	4.4	82	34.3	3	8	53	91
65	9.9	9.0	385	3.3	4.1	81	64.6	8	8	75	92
66	9.9	9.2	512	9.9	9.9	99	999.9	10	5	999	999

Newdata

	epf1	emf1	wessely1	wesp1	wesm1	psqia1	psqib1	psqi61	hsqpf1	hsqrp1
35	999	999	32	21	11	7	0	1	999	999
36	999	999	35	22	15	6	0	0	30	0
37	999	999	30	20	10	10	1	1	999	999
38	100	100	27	22	5	15	1	1	999	999
39	43	40	37	21	16	6	1	0	70	50
40	96	48	28	22	6	5	0	0	999	999
41	88	57	18	13	5	3	0	0	999	999
42	100	100	33	22	11	12	1	1	999	999
43	99	99	99	.	.	5	0	0	15	0
44	88	50	22	17	5	5	0	0	35	0
45	89	87	99	.	.	5	0	0	50	25
46	95	54	29	21	8	8	0	0	55	0
47	94	49	34	22	12	5	0	0	45	999
48	83	86	42	24	18	8	0	1	35	0
49	87	86	28	16	12	7	0	1	40	0
50	86	43	22	16	6	8	0	0	75	50
51	87	92	30	16	14	7	1	0	95	25
52	89	81	32	22	10	6	0	0	35	0
53	90	96	25	14	11	17	1	1	999	999
54	100	100	26	16	10	4	0	0	60	0
55	97	80	35	22	13	6	0	0	999	999
56	93	81	36	20	16	5	0	0	40	0
57	97	58	31	18	13	6	0	0	55	0
58	95	93	39	22	17	9	0	0	50	0
59	100	94	38	24	14	6	1	0	70	0
60	72	50	23	17	6	3	0	0	35	100
61	90	94	31	22	9	1	0	0	30	0
62	88	75	30	19	11	6	0	0	50	0
63	96	70	30	20	10	4	0	0	45	25
64	89	52	25	19	6	6	0	0	35	0
65	92	93	38	23	15	4	0	0	25	0
66	999	999	30	19	11	7	1	1	999	999

Newdata

	hsqbp1	hsqgh1	hsqvi1	hsqsc1	hsqre	hsqme1	baskey1	skida1	skidb1	age2
35	999	999	999	999	999	999	10	0	0	61
36	52	25	20	25	0	64	7	0	0	33
37	999	999	999	999	999	999	10	0	0	29
38	999	999	999	999	999	999	99	0	0	64
39	84	30	35	63	100	80	13	0	0	24
40	999	999	999	999	999	999	6	0	0	27
41	999	999	999	999	999	999	3	0	0	59
42	999	999	999	999	999	999	14	9	0	25
43	0	20	0	13	100	64	19	9	0	30
44	52	62	50	63	100	64	6	0	0	47
45	22	40	15	38	33	40	13	0	0	35
46	41	55	20	75	100	88	6	0	0	40
47	41	15	25	50	67	60	12	0	0	21
48	41	35	25	50	100	56	11	0	0	24
49	22	30	20	25	100	68	7	0	0	29
50	41	40	25	38	100	60	10	0	0	24
51	84	52	45	88	0	52	11	0	0	36
52	31	35	0	0	0	64	13	0	0	53
53	999	999	999	999	999	999	9	0	0	37
54	51	35	5	63	100	68	2	0	0	21
55	999	999	999	999	999	999	10	0	0	51
56	22	35	15	50	33	48	8	0	0	40
57	41	60	30	63	33	92	18	0	0	48
58	62	25	15	13	33	60	8	0	0	32
59	41	72	25	50	33	48	12	0	0	45
60	41	40	35	50	100	68	10	0	0	26
61	61	57	20	13	67	84	12	0	0	33
62	72	20	25	13	100	92	6	0	0	47
63	41	20	25	25	66	64	. 11	0	0	24
64	42	25	25	0	33	60	99	0	0	33
65	84	10	20	13	100	68	16	0	0	99
66	999	999	999	999	999	999	5	0	0	99

	height2	weight2	vo2maxm2	vo2maxl2	vemax2	hrmax2	perhrm2	hrrec2	testd2
35	162.5	75.5	23.3	1.76	70.8	161	89	88	8.0
36	165.5	75.9	27.7	2.11	73.5	173	95	121	10.0
37	170.5	65.2	39.8	2.59	100.8	192	92	118	14.0
38	176.0	52.8	33.3	1.76	65.2	172	100	116	12.0
39	160.5	45.9	44.1	2.03	63.4	172	101	96	11.5
40	164.0	56.7	25.9	1.47	57.1	182	89	120	9.0
41	170.0	89.2	29.8	2.66	85.6	161	95	106	10.5
42	175.5	82.3	28.0	2.28	83.5	191	94	135	8.0
43	177.5	71.1	22.6	1.61	59.3	174	99	114	4.5
44	170.0	67.5	26.2	1.77	63.0	149	92	76	8.0
45	169.0	60.6	33.6	2.00	76.1	187	83	116	12.0
46	163.0	57.8	21.3	1.23	42.9	135	100	76	5.0
47	170.0	53.5	40.2	2.15	88.4	190	72	113	14.0
48	161.0	61.0	40.0	2.41	90.6	175	97	110	12.0
49	160.5	69.2	24.8	1.72	60.0	182	90	86	8.5
50	177.5	57.5	37.7	2.20	85.2	195	95	146	12.5
51	152.0	64.6	34.6	2.19	81.0	179	100	105	15.0
52	162.0	87.7	21.1	1.85	87.7	161	96	105	6.0
53	180.5	83.5	33.7	2.81	97.6	164	91	100	10.5
54	173.0	51.7	31.9	1.65	66.9	186	88	110	13.5
55	169.0	75.6	24.4	1.85	76.2	174	95	114	8.0
56	161.5	62.5	30.4	1.90	69.6	188	98	132	10.0
57	160.0	64.5	26.3	1.70	64.2	186	98	116	11.5
58	176.5	80.7	46.2	3.73	153.1	192	104	124	18.0
59	176.0	73.1	41.2	3.01	125.2	182	100	128	19.0
60	161.0	49.5	35.0	1.73	76.1	190	98	129	12.0
61	164.5	80.1	27.2	2.19	70.0	160	85	104	10.0
62	176.0	91.4	18.9	1.39	93.1	168	94	96	10.0
63	180.0	82.4	27.8	2.29	90.5	202	103	114	12.0
64	164.0	56.7	14.5	1.27	66.4	172	91	112	10.0
65	999.9	999.9	99.9	9.99	999.9	999	.	999	99.9
66	999.9	999.9	99.9	9.99	999.9	999	.	999	99.9

	rpe2	lac142	lac14b2	postlac2	isostr2	fev12	fvc2	ratio2	skf2	hada2
35	61	9.9	7.4	7.5	391	9.9	9.9	99	999.9	2
36	58	2.3	2.3	3.1	219	9.9	9.9	99	999.9	7
37	94	2.2	9.9	7.8	490	3.2	4.1	77	999.9	9
38	63	1.2	9.9	4.0	244	9.9	9.9	99	999.9	8
39	80	1.3	9.9	2.5	464	9.9	9.9	99	999.9	7
40	57	2.6	9.9	8.2	418	3.1	3.9	80	52.9	1
41	72	3.0	2.7	7.2	597	2.8	3.6	79	80.8	2
42	51	3.1	9.9	8.4	382	3.4	3.9	85	106.5	15
43	28	3.7	9.9	5.5	367	3.9	4.7	83	94.2	8
44	64	1.2	2.4	3.1	415	9.9	9.9	99	57.3	99
45	82	1.0	9.9	5.6	326	3.6	4.2	84	51.6	10
46	32	1.0	9.9	2.0	360	9.9	9.9	99	999.9	0
47	83	3.1	9.9	6.6	410	3.4	4.2	82	999.9	4
48	50	1.7	3.4	6.9	347	3.1	4.2	74	999.9	6
49	48	2.7	9.9	4.3	435	2.4	2.9	83	85.4	0
50	46	2.9	7.4	7.4	411	3.6	4.4	83	24.1	7
51	68	3.2	6.1	5.3	284	2.3	2.9	77	999.9	7
52	28	5.2	9.9	8.1	273	2.8	3.4	82	87.0	2
53	39	2.6	2.8	5.3	513	4.0	5.0	80	54.7	10
54	55	3.9	9.9	5.7	332	3.6	3.7	97	27.6	5
55	34	4.4	7.3	10.8	386	2.3	2.7	87	83.8	4
56	51	3.2	9.9	5.7	258	3.2	3.7	83	70.5	11
57	42	2.4	2.9	5.0	252	2.5	3.0	83	72.4	3
58	79	1.2	2.0	9.4	9999	4.1	4.9	84	58.0	6
59	109	1.6	2.0	13.8	596	3.8	4.9	76	44.1	7
60	54	1.6	2.2	6.7	398	2.7	3.2	86	48.8	9
61	63	1.3	1.5	3.8	422	3.1	3.7	84	92.2	1
62	26	2.6	4.2	6.7	376	3.4	4.3	80	85.2	1
63	63	1.0	1.8	6.3	465	3.9	4.9	81	72.2	7
64	26	2.0	3.1	5.5	186	3.5	4.1	85	33.8	9
65	999	9.9	9.9	99.9	9999	9.9	9.9	99	999.9	11
66	999	9.9	9.9	99.9	9999	9.9	9.9	99	999.9	99

	hadd2	pmf2	ppf2	epf2	emf2	wessely	wesp2	wesm2	psqia2	psqib2	psqi6
35	3	45	59	60	35	25	14	11	1	0	0
36	7	87	86	88	87	37	22	13	6	0	0
37	4	23	63	77	52	27	21	6	8	0	1
38	3	69	87	92	84	11	7	4	8	1	0
39	1	73	73	99	81	26	18	8	6	0	1
40	3	52	74	82	53	27	21	6	3	0	0
41	1	56	59	57	46	21	16	5	5	0	0
42	12	96	95	100	93	33	22	11	12	1	1
43	4	999	999	999	999	36	23	13	99	9	9
44	99	999	999	999	999	99	.	.	9	9	9
45	9	63	61	71	65	35	19	16	6	0	0
46	2	94	95	94	90	27	18	9	8	0	0
47	6	92	85	94	56	22	18	6	99	9	0
48	3	71	73	87	78	12	7	5	9	1	0
49	1	55	54	46	46	25	15	10	1	0	0
50	5	36	46	52	35	12	7	5	6	0	0
51	1	25	25	25	74	32	17	15	8	1	0
52	11	88	96	97	84	38	24	14	8	0	0
53	7	67	76	70	80	32	22	10	6	0	0
54	9	54	56	100	73	24	15	9	4	0	0
55	2	23	70	83	50	22	14	8	5	0	0
56	9	74	83	74	75	31	18	13	4	0	0
57	1	25	59	72	22	28	17	11	6	0	0
58	4	83	81	96	95	38	21	17	8	0	1
59	6	67	56	73	74	22	12	10	4	1	0
60	9	74	100	100	61	29	20	9	8	1	0
61	1	81	83	100	96	30	21	9	3	1	0
62	4	85	73	90	84	32	20	12	6	0	0
63	8	65	84	95	70	27	18	9	5	0	0
64	6	51	77	85	50	25	19	6	5	0	0
65	13	85	76	92	84	39	22	7	5	0	0
66	99	999	999	999	999	99	.	.	99	9	9

	hsqpf2	hsqrf2	hsqbp2	hsqgh2	hsqvi2	hsqsf2	hsqre2	hsqmh2	baskey2	skida2
35	999	999	999	999	999	999	999	999	6	0
36	999	999	999	999	999	999	999	999	99	0
37	70	0	41	15	45	75	100	60	12	0
38	90	75	74	35	60	75	33	64	7	0
39	45	0	44	35	25	50	100	80	12	0
40	55	25	90	40	35	63	100	80	7	0
41	80	25	90	65	45	75	100	92	5	0
42	30	0	62	20	20	100	0	24	13	9
43	35	0	0	20	5	13	100	68	3	99
44	70	25	84	65	60	75	100	76	99	99
45	60	0	22	30	35	38	0	40	13	0
46	45	0	22	40	5	50	100	88	5	0
47	50	0	31	20	15	50	33	40	6	0
48	45	0	52	67	50	50	33	84	10	99
49	90	25	62	35	55	63	100	88	3	0
50	70	75	64	47	60	63	100	84	10	99
51	100	25	42	65	70	50	67	56	14	99
52	35	0	41	25	0	13	100	72	14	2
53	40	50	51	40	40	75	100	64	8	0
54	55	50	90	57	40	88	100	77	0	0
55	25	0	62	40	45	38	33	60	5	0
56	50	25	62	45	45	75	66	84	5	0
57	55	50	44	40	65	100	100	92	18	0
58	65	0	72	40	35	38	33	52	8	0
59	95	50	74	97	55	88	100	72	6	0
60	25	0	2	25	35	50	100	64	12	0
61	25	0	51	57	5	25	100	92	11	0
62	40	0	90	30	15	13	0	88	7	0
63	45	25	51	15	30	50	100	76	8	0
64	65	25	90	52	50	63	100	84	8	0
65	45	0	54	999	25	25	33	48	99	9
66	999	999	999	999	999	999	999	999	99	99

Newdata

	skidb2	cgio2	cgid2	cgip2	cgi2full	age3	height3	weight3	vo2maxm3
35	0	9	2	2	3	99	999.9	999.9	99.9
36	0	9	2	2	3	33	165.5	74.5	27.7
37	0	1	2	2	3	30	170.5	65.3	39.5
38	0	9	2	2	3	64	176.0	56.2	33.9
39	0	2	1	2	3	24	161.0	46.0	37.4
40	0	1	1	2	3	28	164.0	58.8	27.8
41	0	1	1	1	2	59	170.0	90.2	29.0
42	0	4	2	2	6	26	175.5	79.0	29.7
43	99	9	9	2	4	30	175.5	73.5	21.5
44	99	9	9	2	4	99	999.9	999.9	99.9
45	0	1	2	2	4	99	999.9	999.9	99.9
46	0	9	2	2	3	99	999.9	999.9	99.9
47	0	4	2	2	3	99	999.9	999.9	99.9
48	99	9	2	2	3	25	161.0	60.4	33.1
49	0	9	1	1	2	29	160.0	71.7	26.1
50	99	9	2	2	3	99	999.9	999.9	99.9
51	99	9	1	1	2	37	152.0	66.4	31.7
52	0	4	2	2	3	99	999.9	999.9	99.9
53	0	4	2	2	3	38	180.5	84.9	35.6
54	0	2	1	1	1	21	173.0	52.2	39.1
55	0	1	1	1	2	51	169.0	76.1	27.8
56	0	3	1	1	2	40	161.5	63.7	31.5
57	0	3	1	1	2	48	160.0	62.4	18.0
58	0	2	2	2	3	32	176.0	83.4	46.0
59	0	1	1	1	1	46	176.0	68.6	38.0
60	0	3	2	2	3	27	161.0	50.4	35.4
61	0	9	2	2	3	33	164.5	82.7	28.7
62	0	4	2	2	3	48	176.0	89.8	23.0
63	0	3	2	2	3	24	180.0	82.3	28.6
64	0	4	2	2	9	99	999.9	999.9	99.9
65	0	9	1	1	9	99	999.9	999.9	99.9
66	99	9	9	9	9	99	999.9	999.9	99.9

	vo2maxl3	vemax3	hrmax3	hrrec3	testd3	rpe3	lac143	lac14b3	postlac3
35	9.99	999.9	999	999	99.9	999	9.9	9.9	99.9
36	2.06	74.5	187	126	12.0	56	6.4	9.9	7.6
37	2.58	92.9	190	116	14.0	92	2.5	4.5	10.0
38	1.90	71.1	179	110	12.0	61	1.7	3.0	4.9
39	1.72	63.9	169	104	12.5	85	1.2	1.2	3.2
40	1.63	64.7	182	120	8.0	56	1.8	9.9	7.2
41	2.60	90.8	167	111	8.0	68	4.0	4.0	7.6
42	2.34	102.7	187	123	8.0	51	4.6	9.9	8.4
43	1.58	56.3	173	121	5.5	24	2.6	4.8	4.9
44	9.99	999.9	999	999	99.9	999	9.9	9.9	99.9
45	9.99	999.9	999	999	99.9	999	9.9	9.9	99.9
46	9.99	999.9	999	999	99.9	999	9.9	9.9	99.9
47	9.99	999.9	999	999	99.9	999	9.9	9.9	99.9
48	2.00	79.4	168	107	12.5	43	2.2	9.9	6.5
49	1.72	53.3	175	92	9.5	44	2.5	4.6	6.7
50	9.99	999.9	999	999	99.9	999	9.9	9.9	99.9
51	2.10	74.0	181	92	12.0	72	3.6	4.0	5.3
52	9.99	999.9	999	999	99.9	999	9.9	9.9	99.9
53	3.02	121.5	167	116	12.0	37	2.2	5.2	6.3
54	2.04	79.1	199	122	16.0	54	2.1	9.9	7.1
55	2.12	71.7	173	110	8.0	35	3.9	4.6	6.3
56	2.00	67.6	178	103	11.0	48	2.4	3.5	99.9
57	1.13	61.2	174	107	9.0	51	3.2	9.9	3.8
58	3.80	146.0	194	114	18.0	85	2.2	2.3	9.6
59	2.65	97.9	163	103	16.0	104	1.8	2.6	7.3
60	1.78	83.0	189	136	12.0	54	1.1	9.9	5.3
61	2.38	80.7	174	112	10.0	57	1.2	1.0	3.6
62	2.07	105.2	159	100	9.0	26	1.3	2.3	6.0
63	2.35	87.8	210	104	12.8	59	1.5	1.4	4.8
64	9.99	999.9	999	999	99.9	999	9.9	9.9	99.9
65	9.99	999.9	999	999	99.9	999	9.9	9.9	99.9
66	9.99	999.9	999	999	99.9	999	9.9	9.9	99.9

Newdata

	isostr3	fev13	fvc3	ratio	skf3	hada3	hadd3	pmf3	ppf3	epf3	emf3
35	9999	9.9	9.9	99	999.9	99	99	999	999	999	999
36	328	1.8	2.4	74	999.9	99	99	999	999	999	999
37	682	3.3	4.4	75	999.9	5	2	33	72	95	78
38	272	2.5	3.3	74	999.9	8	8	74	84	93	72
39	492	9.9	9.9	99	999.9	6	1	77	70	94	96
40	453	3.3	4.1	78	999.9	5	2	44	75	43	24
41	555	2.7	3.4	79	89.0	1	1	59	59	68	46
42	333	3.3	3.8	88	104.9	11	9	98	99	92	97
43	9999	3.8	4.4	86	91.2	5	5	89	97	91	99
44	9999	9.9	9.9	99	999.9	99	99	999	999	999	999
45	9999	9.9	9.9	99	999.9	99	99	999	999	999	999
46	9999	9.9	9.9	99	999.9	99	99	999	999	999	999
47	9999	9.9	9.9	99	999.9	99	99	999	999	999	999
48	283	3.4	4.1	83	55.6	7	9	25	73	85	75
49	313	2.7	3.0	90	999.9	7	6	53	54	51	52
50	9999	9.9	9.9	99	999.9	99	99	999	999	999	999
51	286	2.0	2.6	75	67.8	9	7	93	69	39	82
52	9999	9.9	9.9	99	999.9	99	99	999	999	999	999
53	527	4.0	5.1	79	999.9	8	6	87	79	86	89
54	361	3.7	3.8	95	28.5	4	7	50	50	65	50
55	344	2.4	2.8	84	100.6	4	7	65	80	77	58
56	268	2.9	3.9	74	70.4	8	8	64	66	62	50
57	273	2.5	3.1	80	65.8	2	1	18	83	93	39
58	852	4.0	4.7	85	45.0	9	6	72	76	90	91
59	568	3.7	4.8	78	33.6	2	1	51	54	73	56
60	325	2.9	3.3	88	53.7	12	10	95	96	100	99
61	270	2.9	3.5	82	84.6	7	7	61	65	80	86
62	425	3.6	4.5	80	99.8	8	5	51	72	84	51
63	458	4.1	4.9	83	74.2	3	2	56	74	72	52
64	9999	9.9	9.9	99	999.9	99	99	999	999	999	999
65	9999	9.9	9.9	99	999.9	99	99	999	999	999	999
66	9999	9.9	9.9	99	999.9	99	99	999	999	999	999

Newdata

	wessely3	wesp3	wesm3	psqia3	psqib3	psqi63	hsqpf3	hsqrp3	hsqbp	hsqgh3
35	99	.	.	99	9	9	999	999	999	999
36	99	.	.	99	9	9	999	999	999	999
37	31	22	9	7	0	1	60	0	62	20
38	16	8	8	9	1	1	80	25	74	45
39	99	.	.	99	9	9	999	999	999	999
40	24	19	5	3	0	0	65	25	90	52
41	20	15	5	3	0	0	80	50	90	67
42	33	22	11	11	1	1	25	0	22	25
43	5	1	2	5	0	0	40	0	12	30
44	99	.	.	99	9	9	999	999	999	999
45	99	.	.	99	9	9	999	999	999	999
46	99	.	.	9	9	9	999	999	999	999
47	99	.	.	99	9	9	999	999	999	999
48	13	6	5	3	0	0	65	0	41	52
49	20	10	10	2	0	0	85	100	84	45
50	99	.	.	9	9	9	999	999	999	999
51	30	16	14	10	1	0	95	0	31	57
52	99	.	.	99	9	9	999	999	999	999
53	27	15	12	10	0	1	45	75	61	50
54	18	9	9	2	0	0	75	100	90	72
55	30	18	12	6	0	0	40	0	52	52
56	25	16	9	4	0	0	55	75	62	67
57	32	19	13	8	0	1	55	0	31	62
58	30	18	12	8	0	1	75	0	82	40
59	22	14	8	3	0	0	95	100	84	97
60	35	19	16	6	0	0	30	0	12	15
61	24	16	8	4	1	0	50	0	72	30
62	30	19	11	7	0	0	65	0	9	35
63	25	15	10	5	1	0	65	50	31	75
64	99	.	.	99	9	9	999	999	999	999
65	99	.	.	99	9	9	999	999	999	999
66	99	.	.	99	9	9	999	999	999	999

	hsqvi3	hsqsf3	hsqre3	hsqmh3	baskey3	skida3	skidb3	cgio3	cgid3	cgip3
35	999	999	999	999	99	99	99	9	9	9
36	999	999	999	999	99	0	0	9	2	2
37	40	38	67	67	10	0	0	1	3	3
38	50	63	33	44	7	0	0	1	2	2
39	999	999	999	999	99	0	0	9	9	3
40	45	75	100	84	4	0	0	9	9	3
41	55	75	100	92	2	0	0	1	2	2
42	5	13	33	52	15	9	0	3	3	3
43	10	13	100	68	16	9	0	9	9	4
44	999	999	999	999	99	99	99	9	9	9
45	999	999	999	999	99	99	99	9	9	9
46	999	999	999	999	99	99	99	9	9	9
47	999	999	999	999	99	99	99	9	9	9
48	40	50	67	44	5	0	0	9	2	2
49	70	100	100	88	2	99	99	9	1	1
50	999	999	999	99	99	99	99	9	9	9
51	30	38	0	40	13	99	99	9	9	3
52	999	999	999	999	99	2	0	9	4	3
53	25	50	100	80	7	0	0	9	9	9
54	70	100	100	88	3	0	0	9	1	1
55	30	38	33	60	9	0	0	1	1	1
56	45	100	66	76	4	0	0	2	2	2
57	30	50	100	68	18	0	0	4	4	4
58	40	38	100	76	5	0	0	3	3	3
59	70	100	100	64	7	0	0	1	1	1
60	0	38	33	36	12	2	9	4	5	5
61	15	50	100	88	12	0	0	9	3	3
62	25	38	100	88	6	0	0	4	3	2
63	30	75	100	80	6	0	0	3	2	2
64	999	999	999	999	99	99	99	9	9	9
65	999	999	999	999	99	99	99	9	9	9
66	999	999	999	999	99	99	99	9	9	9

Newdata

	age4	height4	weight4	vo2maxm4	vo2maxl4	vemax4	hrmax4	hrrec4	testd4
35	99	999.9	999.9	99.9	9.99	999.9	999	999	99.9
36	33	165.5	76.1	24.1	1.84	61.5	172	108	8.5
37	30	170.5	65.6	44.0	2.89	102.7	192	116	14.0
38	65	176.0	54.9	38.9	2.14	82.1	171	125	15.0
39	99	999.9	999.9	99.9	9.99	999.9	999	999	99.9
40	29	164.5	58.4	28.3	1.65	55.9	177	108	8.5
41	60	170.0	88.5	32.9	2.91	100.6	177	117	12.0
42	26	175.5	81.2	27.4	2.22	95.3	192	132	8.0
43	30	178.0	74.1	24.7	1.83	68.0	179	124	6.5
44	99	999.9	999.9	99.9	9.99	999.9	999	999	99.9
45	99	999.9	999.9	99.9	9.99	999.9	999	999	99.9
46	99	999.9	999.9	99.9	9.99	999.9	999	999	99.9
47	99	999.9	999.9	99.9	9.99	999.9	999	999	99.9
48	25	161.5	59.4	37.2	2.24	94.0	179	115	14.0
49	30	159.0	72.1	33.4	2.07	63.9	185	98	10.0
50	99	999.9	999.9	99.9	9.99	999.9	999	999	99.9
51	37	152.0	68.9	28.6	1.97	73.3	169	93	11.0
52	99	999.9	999.9	99.9	9.99	999.9	999	999	99.9
53	99	999.9	999.9	99.9	9.99	999.9	999	999	99.9
54	21	173.0	51.8	41.2	2.13	84.2	197	124	17.0
55	51	169.0	76.5	25.0	2.03	73.4	163	105	8.0
56	40	161.5	62.5	33.6	2.10	66.6	186	115	11.0
57	48	160.0	64.1	17.1	1.10	67.7	192	136	9.5
58	32	176.0	83.4	40.2	3.36	127.6	194	123	18.0
59	46	176.0	68.1	40.0	2.72	100.4	176	120	18.0
60	27	161.0	48.0	21.8	1.08	50.7	167	92	8.0
61	33	164.5	79.4	28.4	2.25	82.1	188	108	11.0
62	48	176.0	93.7	21.8	2.04	114.7	174	110	10.0
63	25	180.0	84.0	20.2	1.70	99.2	212	130	12.0
64	99	999.9	999.9	99.9	9.99	999.9	999	999	99.9
65	99	999.9	999.9	99.9	9.99	999.9	999	999	99.9
66	99	999.9	999.9	99.9	9.99	999.9	999	999	99.9
67	99	999.9	999.9	99.9	9.99	999.9	999	999	99.9
68	99	999.9	999.9	99.9	9.99	999.9	999	999	99.9

	rpe4	lac144	lac14b4	postlac4	isostr4	fev14	fvc4	ratio4	skf4	hada4
35	99	9.9	9.9	99.9	9999	9.9	9.9	99	999.9	99
36	62	1.6	1.8	1.9	276	1.9	2.5	77	999.9	99
37	90	4.0	4.0	10.2	675	3.3	4.2	77	999.9	4
38	51	1.6	2.6	5.2	394	2.7	3.7	73	18.7	6
39	999	9.9	9.9	99.9	9999	9.9	9.9	99	999.9	99
40	56	.9	1.7	5.5	409	3.6	4.1	88	53.0	6
41	66	3.0	3.2	9.6	592	2.7	3.4	79	90.5	6
42	56	4.9	9.9	9.6	300	3.6	3.9	91	106.4	11
43	21	2.0	9.9	4.9	465	3.2	3.7	92	86.6	3
44	999	9.9	9.9	99.9	9999	9.9	9.9	99	999.9	99
45	999	9.9	9.9	99.9	9999	9.9	9.9	99	999.9	99
46	999	9.9	9.9	99.9	9999	9.9	9.9	99	999.9	99
47	999	9.9	9.9	99.9	9999	9.9	9.9	99	999.9	99
48	39	1.8	2.6	6.5	403	3.4	4.1	83	56.1	8
49	42	3.0	9.9	6.5	300	2.6	2.9	89	999.9	7
50	999	9.9	9.9	99.9	9999	9.9	9.9	99	999.9	99
51	68	4.7	3.7	3.5	308	2.3	2.7	85	68.7	8
52	999	9.9	9.9	99.9	9999	9.9	9.9	99	999.9	99
53	999	9.9	9.9	99.9	9999	9.9	9.9	99	999.9	99
54	49	2.1	2.5	6.8	334	3.6	3.7	95	27.6	2
55	34	4.0	6.0	8.7	379	2.5	2.6	94	999.9	4
56	51	1.2	1.7	5.2	356	3.2	3.8	85	66.3	10
57	68	2.3	9.9	6.2	258	2.6	3.1	82	78.6	1
58	80	1.8	9.9	7.7	726	4.0	4.7	85	41.8	8
59	89	2.7	9.9	7.6	552	3.7	4.9	76	31.2	7
60	62	1.3	9.9	1.8	357	2.6	2.9	90	40.1	12
61	51	2.1	2.4	5.1	257	3.2	3.7	86	89.0	6
62	22	6.0	6.3	10.2	331	3.6	4.6	78	75.2	8
63	78	2.4	4.9	7.5	454	4.1	4.9	84	99.4	3
64	999	9.9	9.9	99.9	9999	9.9	9.9	99	999.9	99
65	999	9.9	9.9	99.9	9999	9.9	9.9	99	999.9	99
66	999	9.9	9.9	99.9	9999	9.9	9.9	99	999.9	99
67	999	9.9	9.9	99.9	9999	9.9	9.9	99	999.9	99
68	999	9.9	9.9	99.9	9999	9.9	9.9	99	999.9	99

	hadd4	pmf4	ppf4	epf4	emf4	wessely4	psqia4	psqib4	psqi64	hsqpf4
35	99	999	999	999	999	99	99	9	9	999
36	99	999	999	999	999	99	99	9	9	999
37	7	999	999	999	999	99	99	9	9	999
38	7	50	50	50	50	10	10	1	0	95
39	99	999	999	999	999	99	99	9	9	75
40	7	47	73	85	49	26	3	0	0	55
41	6	50	55	55	50	11	5	0	0	80
42	10	98	90	95	97	34	11	1	0	40
43	6	71	72	91	93	3	7	0	0	45
44	99	999	999	999	999	99	99	9	9	999
45	99	999	999	999	999	99	99	9	9	999
46	99	999	999	999	999	99	99	9	9	999
47	99	999	999	999	999	99	99	9	9	999
48	10	34	60	59	55	14	3	0	0	65
49	4	50	48	57	50	1	3	0	0	100
50	99	999	999	999	999	99	9	9	9	999
51	10	24	27	42	61	19	8	1	0	95
52	99	999	999	999	999	99	99	9	9	999
53	99	999	999	999	999	99	99	9	9	999
54	1	50	50	50	50	18	2	0	0	80
55	4	50	62	63	53	31	9	1	0	40
56	6	55	55	77	76	12	3	0	0	70
57	1	50	72	94	51	27	5	0	0	60
58	5	65	65	63	67	28	6	0	0	85
59	6	52	50	57	57	17	0	0	0	95
60	8	63	100	96	75	24	7	0	1	35
61	7	71	80	90	84	27	1	0	0	60
62	5	57	66	66	56	25	10	0	1	60
63	1	52	61	65	55	23	4	0	0	75
64	99	999	999	999	999	99	99	9	9	999
65	99	999	999	999	999	99	99	9	9	999
66	99	999	999	999	999	99	99	9	9	999
67	99	999	999	999	999	99	99	9	9	999
68	99	999	999	999	999	99	99	9	9	999

	hsqrp4	hsqbp4	hsqgh4	hsqvi4	hsqsf4	hsqre4	hsqmh4	baskey4	skida4
35	999	999	999	999	999	999	999	99	99
36	999	999	999	999	999	999	999	99	0
37	999	999	999	999	999	999	999	99	2
38	75	84	35	50	88	67	76	0	0
39	50	54	40	30	63	100	80	99	0
40	50	90	47	35	63	100	84	6	0
41	75	90	52	60	100	999	76	6	0
42	0	52	25	10	38	33	52	14	9
43	0	10	30	20	38	100	76	17	99
44	999	999	999	999	999	999	999	99	99
45	999	999	999	999	999	999	999	99	99
46	999	999	999	999	999	999	999	99	99
47	999	999	999	999	999	999	999	99	99
48	0	41	52	40	50	66	44	11	0
49	100	90	67	80	100	100	96	2	99
50	999	999	999	999	999	999	999	99	99
51	100	52	67	70	88	33	60	11	99
52	999	999	999	999	999	999	999	99	99
53	999	999	999	999	999	999	999	99	0
54	100	90	77	90	100	100	96	0	0
55	0	74	50	50	50	33	76	4	0
56	75	74	77	85	80	66	67	5	0
57	0	31	67	35	100	100	100	19	0
58	0	74	45	50	50	66	84	5	0
59	100	84	100	75	100	100	84	4	0
60	25	47	15	15	38	33	44	8	9
61	0	62	72	15	50	100	84	16	0
62	0	84	40	30	13	100	92	5	0
63	50	41	15	55	63	100	92	6	0
64	999	999	999	999	999	999	999	99	99
65	999	999	999	999	999	999	999	99	9
66	999	999	999	999	999	999	999	99	99
67	999	999	999	999	999	999	999	99	99
68	999	999	999	999	999	999	999	99	99

	skidb4	cgio4	cgid4	cgip4
35	99	9	9	3
36	0	9	2	2
37	0	9	4	4
38	0	9	3	3
39	0	9	9	9
40	0	9	9	9
41	0	9	9	2
42	0	3	3	3
43	99	9	9	9
44	99	9	9	9
45	99	9	9	9
46	99	9	9	9
47	99	9	9	9
48	0	9	9	9
49	99	9	1	1
50	99	9	9	9
51	99	9	9	1
52	99	9	9	9
53	0	9	5	5
54	0	1	1	1
55	0	9	2	3
56	0	9	1	1
57	0	4	4	3
58	0	2	1	1
59	0	1	1	1
60	0	2	2	2
61	0	3	2	2
62	0	2	2	1
63	0	3	2	2
64	99	9	9	9
65	0	2	2	9
66	99	9	9	9
67	99	9	9	9
68	99	9	9	9