Chronic fatigue syndrome (CFS) has been recognized as an illness since the development of a working case definition under the leadership of the Centers for Disease Control (CDC) in 1988 [1,2]. According to this definition CFS is an illness characterized by extreme persistent and disabling fatigue of unknown origin that is present for at least 6 months and that is not alleviated by rest. The diagnosis CFS can be made only after alternative medical and psychiatric causes of chronic fatiguing illness have been excluded [1,2]. The fatigue is severe enough to substantially reduce the patients ability to perform daily activities and results in moderate to severe disability [3]. CFS is a controversial diagnosis of exclusion that cannot be confirmed by laboratory tests. Classifying and characterizing patients with CFS has been a challenge as it is most likely a heterogeneous syndrome with many potential causes, and not a homogenous disease with one underlying organic defect [3]. This makes estimates of prevalence difficult, subjective and variable among different populations. A range has been reported from 37 cases per 100 000 in an Australian population [4] and up to 1088 per 100 000 in a sample of American nurses [5]. Reported risk factors for a poor prognosis are older age, more chronic immobilizing illness (bed rest), having a comorbid psychiatric disorder and holding a belief that the illness is the result of physical causes [6]. Jason et al. [5] suggested that stress may increase the risk of developing CFS, which may make CFS into a gradually increasing illness since the development of a working case definition. McCully and Natelson [7] recognized this contingency and, therefore, rightly indicate that future research is required to underpin their conclusions and to investigate whether the observed abnormalities are the cause or the consequence of CFS.

However, there also is a body of already published physiological evidence which seems to suggest that deconditioning plays an important, and so far underappreciated, role in the abnormal physiology that is seen in CFS patients. Saltin et al. [9] have shown that 20 days of bed rest by healthy subjects reduced cardiac output and oxygen delivery to working muscles by 15–20%. Muscle blood flow during and following exercise is also reduced in elderly subjects [10]. This has, in part, been explained by a reduced vasodilatory capacity and in part by the decreased capillarization, which again is a consequence of the reduction in physical activity and deconditioning that are seen during ageing [10]. The development of abnormal autonomic or peripheral control of muscle blood flow is not limited to CFS patients [7,11] but also occurs in healthy subjects in the adaptation period to acute and long-term deconditioning. For this reason the control group is extremely important in studies attempting to define abnormalities that are specific for CFS. In most reports on CFS patients the control group has not been matched for physical activity level. McCully and Natelson [7] matched the healthy controls for age and height but not for physical activity levels. The mean weight of the CFS patients was about 9 kg greater than that of the control group, indicating that the patients were potentially less active and deconditioned. Future comparisons of CFS patients and controls, for this reason, should include estimates of physical activity and/or working capacity and/or muscle mitochondrial density/concentration (see below).

Wagenmakers and colleagues [12,13] obtained muscle biopsies from 23 patients who, according to current criteria, were classified as suffering from CFS or fibromyalgia. Fibromyalgia is a syndrome that overlaps with CFS. The activity of four mitochondrial enzymes was generally lower in the biopsies of the patients than in those of normal, healthy controls, but the range was wide...
(30–100% of the mean value of the control range; controls were untrained volunteers from the research department). These data indicate that some, but not all, patients with CFS show a severe loss of mitochondria. Six of the patients with the lowest mitochondrial activities performed a graded incremental exercise test on a cycle ergometer and had a dramatically reduced exercise capacity (maximal work rate 60–120 W; 20–50% of the normal controls). They nevertheless achieved heart rates and blood lactate concentrations normally found with maximal exercise [12,13]. These data indicate that these patients showed a metabolic adaptation to severe deconditioning, and that the adaptation to deconditioning may be as large as, but the reverse of that reported in trained subjects [14,15]. This implies that these patients experience the stress of maximal exercise during normal daily activities (20–80 W) and this again provides a reason to avoid exercise, so that they spiral down in a vicious circle of inactivity and exercise intolerance [12].

One of the consequences of low mitochondrial density is a reduced oxidative capacity. This again leads to a reduced rate of resynthesis of creatine phosphate following high-intensity exercise [16]. Deconditioning of the CFS patients in the McCully and Natelson [7] study, leading to a low mitochondrial density in muscle, thus presents a potential alternative explanation (besides the lack of oxygen supply, as suggested by the authors) for the observed reduction in the resynthesis rate of creatine phosphate following exercise.

Deconditioning per se leads not only to biochemical adaptation in the muscle (lower content of mitochondria) but also to many of the symptoms reported by patients with CFS [1,2]. Newman and Edwards [17] reported, in 1979, that subjects with low habitual activity and a dislike of exercise developed so-called ‘effort syndrome’ symptoms. These, among others, include tachycardia, palpitations, dizziness (especially following exercise), disturbances of consciousness and vision, breathlessness, muscular pains, tremor, autonomic disturbances such as excessive sweating of the palms of the hands, orthostatic disturbances, fatigue, subjective weakness, headaches, tension and anxiety. Human volunteers subjected to hypokinesia as part of a space research programme complained of symptoms that were strikingly similar [18]. Finally, patients with a dramatically reduced exercise tolerance due to a defined muscle disease, e.g. McArdle’s disease (muscle glycogen phosphorylase deficiency), who choose to avoid exercise also develop CFS and effort syndrome symptoms and, as a consequence, become disabled, whereas those patients who choose to remain active despite the pain and discomfort of exercise do not develop such symptoms and manage to remain successful in their profession [12,13]. Together, these findings seem to suggest that the abnormal physiology that has been reported in CFS by McCully and Natelson [7] and many others may well be the consequence of the deconditioning and lack of exercise of CFS patients, rather than the underlying organic cause of CFS.

Therefore, as an exercise physiologist, I end with the conclusion that it is time that the highly customized exercise programmes that have been suggested to be of potential therapeutic benefit for CFS patients [3] are brought into practice. They may not help all patients, but positive effects may certainly be expected for those who have succumbed to the vicious circle of progressive inactivity and exercise intolerance. I also suspect that the prevalence of CFS may well be reduced substantially if society in general becomes more active and follows the advice of experienced exercise physiologists, which is that man is a machine which is supposed to work, run, cycle and play in order to maintain a healthy functioning body and mind. However, the gradual decrease in daily physical activity seen in modern society may have the opposite effect and make CFS a serious health threat for the twenty-first century.

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REFERENCES