The Enigma of Chronic Fatigue

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Key Words
Chronic fatigue • Fatigue assessment • Neurasthenia

Abstract
Until new, reproducible criteria are established, the ubiquitous ‘chronic fatigue state’ emerges as a non-specific complaint shared by many different entities. Presently, it is neither a valid nor a verifiable medical diagnosis.

Introduction

The Oxford English Dictionary defines fatigue as lassitude or weariness resulting from either bodily or mental exertion; or physiologically as a condition of muscles, organs, or cells characterized by a temporary reduction in power or sensitivity following a period of prolonged activity or stimulation. This paper questions its employment as a valid medical diagnosis.

History

A 1966 Lancet editorial recounted that in the 16th century, 'Fatigue' first appeared as a description of tedious duty [1]. In the early 19th century, 'the delicate and easily exhausted upper class was succeeded by the hardworking lower classes, who laboured under a Protestant work ethic. The accompanying lifestyle of the industrial revolution machinery induced noise, excitement and a fear of accidents' [1]. In 1857, the French physician E.A. Duschene (cited by Barnett [2]) identified the 'maladie des mecaniciens'. Victorian doctors regarded the soul as something that could be exhausted by overuse or over-stimulation of body or mind. Fatigue was not just physical, but also mental [3]. ‘Neurasthenia’ was a descriptive term coined by George Miller Beard [4] for what was colloquially known as ‘nervous exhaustion’ – commonplace in the 19th century; the word has the merits of simplicity and its meaning is self-evident. A celebrated example was the philosopher and psychologist Herbert Spencer. In his later years, dogged by fatigue and depression, ‘The retreat into illness was also for Spencer a retreat from social intercourse’ [5].

The concept of neurasthenia declined between the 1930s and 1960s. But curiously, in the 1980s, when the term ‘chronic fatigue’ emerged as a medical term, neurasthenia was not replaced but reappeared. The symptoms of fatigue were modern variants of neurasthenia, which had ‘adopted the organic inheritance of Beard’s ideas of neurasthenia, despite the fact that the question of organicity could not be decisively answered in a single case’ [6].

In both World Wars, combat fatigue was a nervous disorder resulting from prolonged or severe battle experience. In modern times, fatigue worryingly appears to be burgeoning in the healthy population, and cultural trends uncover the symptom as a common complaint that on enquiry often closely relates to a state of boredom, especially in teenagers. Yet, the intensity of complaints is no less severe in teenage boredom than in illness: ‘Fatigue is more than tiredness – pathological exhaustion, perhaps – and in its medical sense it has been associated with modernity, with fear of the new’ [2].
Analysis of tiredness or fatigue is a vexing problem. In contrast to blood glucose or pulse rate, fatigue is immeasurable. Management is hampered by the uncertainty of its cause and the lack of specific treatment. The complaint of tiredness or fatigue is recorded in almost all medical illnesses, ranging from acute and chronic infections to heart, kidney and respiratory failure, and every variety of cancer, neoplastic diseases and their treatments. Degenerative diseases of the nervous system are similarly often complicated by fatigue. Although common in advanced disease when physical disability, pain, sleeplessness, loss of morale and reactive depression are frequent [e.g. in arthritis, multiple sclerosis (MS), Parkinsonism, stroke, ankylosing spondylitis, systemic lupus erythematosus], it can occur in non-disabled patients in the early stages of illness. Fatigue, both physical and mental, is also prominent in a variety of anxiety and depressive illnesses and has attracted the dubious term ‘mild astheno-emotional disorder’ [7] to characterize it. Fatigue can diminish both the quality of life and physical function.

Because its significance in the individual is difficult to assess, it is essential to ascertain a baseline, i.e. the prevalence of the symptom in the healthy population.

**Clinical Setting**

In a cross-sectional questionnaire study in the Danish general population (a random, age-stratified sample of 1,608 people aged 20–77 years), five fatigue scales were appraised [8]. Fatigue was classed as: General, Physical, Reduced activity, Reduced motivation, or Mental, with overall positive scores for 18–35% of the population. Severe tiredness was more common in females though gender differences were generally small. General and Mental fatigue decreased linearly with age. Depressed respondents scored substantially higher on all scales, especially on Mental fatigue. Respondents with low social status and depression had high fatigue scores on all scales, independent of other factors. The effect of somatic disease depended on age, gender and/or whether the person was living alone. Physical and mental diseases play essential parts for the level of fatigue and as modulators of the associations between sociodemographic factors and fatigue.

Another recent study, by Furberg et al. [9], concludes: ‘Prevalence for different definitions of self-reported lifetime fatigue ranged from 36.7% for any fatigue to 2.7% for chronic fatigue syndrome-like illness. Females were two to three times more likely to report fatigue than males ...’ People with lifetime fatigue had more compromised functional status than people without lifetime fatigue. Self-reported lifetime fatiguing illness varied widely depending upon the definitions adopted.’

**Difficulties in Assessing Fatigue**

We must therefore start by accepting that tiredness or a sense of fatigue are commonplace normal experiences [10]. As Giovanni [10] reasonably says, ‘It is a subjective feeling of tiredness or exhaustion which could refer to both physical (motor activities) and mental (cognitive or emotional) processes’.

The complex sensations may result from the physiological fatigue of temporary lack of sleep, strenuous exertion, or the converse state of physical inertia and mental boredom. But the reliability and applicability of epidemiological data to the individual is questionable. Definition remains controversial, arbitrary, but important.

Fatigue and fatigability are in themselves not pathological. ‘Fatigue’ simply refers to being tired or unable to maintain expected force. ‘Fatigability’ is a measure of how easily someone feels tired. Fatigue may describe many experiences, from the exhaustion of a marathon to the sleepiness following prolonged wakefulness. Crucially, the complaints of mental and physical fatigue often fail to correlate with cognitive function or physical muscle fatigue. For example, patients with chronic fatigue syndrome (CFS) describe feelings of muscle weariness or tiredness unrelated to objective measures of muscle fatigue [11]. In a separate study, DeLuca et al. [12] found that the CFS group did not differ from the control subjects on tasks of cognitive functioning (e.g., memory), even though they showed a high degree of subjective complaint of cognitive impairment.

Some authorities assert that, ‘true fatigue and ... tiredness are plainly different’, or ‘fatigue is more than tiredness’ and refer to ‘pathological exhaustion’ [2]. The accuracy of these assertions is doubtful. The stoical denials of tiredness or its too easy assertion, determine how patients, questionnaire respondents and physicians use the words. Does ‘exhaustion’, as cited above imply that an athlete’s transient, physiological exhaustion is abnormal? Some argue that fatigue is only pathological if it is disabling – that is, if it affects a person’s social, physical and occupational wellbeing. But that criterion, too, incorpo-
rates a large subjective element in which the sufferer defines his/her own threshold for distinguishing when it is or is not disabling. For want of a satisfactory definition, the Centres for Disease Control and Prevention (CDC) defined ‘profound fatigue’, which they imply is ‘pathological fatigue’; in the context of CFS as, ‘... [fatigue] not improved by bed rest and that may be worsened by physical or mental activity’ [13].

There has been criticism of these criteria. For example, Dale and Straus [14] pointed out that some psychiatric illnesses could be secondary to prolonged fatigue and that the CDC criteria did not clearly define when psychiatric illness is an exclusion criteria or when it is a defining criterion. Only the group with a chronic psychiatric illness that preceded the development of chronic fatigue was excluded (table 1). The UK (Oxford) criteria [15] have also not escaped criticism.

**Fatigue in Neurological Disease**

Two different symptom phenomena should be distinguished. One is muscle tiredness succeeding exertion (‘peripheral fatigue’); the other is a more general loss of energy, disinclination to move often described as weariness, lassitude, or anergia (labelled ‘central fatigue’). Appraisal of neurological (i.e. central) diseases might in theory point to a mechanism of central fatigue. About 50–80% of subjects with MS have fatigue and in half of them it is their most disabling symptom. However, Krupp et al. [16] showed that fatigue was largely independent of self-reported depressive symptoms in MS. But the increased attention given to MS patients with fatigue during investigations has been noted to improve the symptom, suggesting psychosomatic factors. Similarly, in treatment studies of MS, Krupp et al. [17] and the Canadian MS Research Group [18] noticed a decline in fatigue severity for all patients between their first and second study visits, ‘even before starting treatment’.

MS patients, who have normal baseline strength on testing, develop greater ‘physiological’ fatigue during maximal sustained contraction (adductor pollicis), which is considered central in origin. However, there is no correlation between the amount of inducible fatigue and that of fatigue experienced in everyday life, suggesting that other factors contribute to this symptom. Despite subjective central fatigue, there is no central motor dysfunction as tested by transcranial magnetic stimulation, and no firm evidence of frequency-dependent conduction block, which might generate physiological fatigue [19]. The absence of a demonstrable increase in motor pathway dysfunction, Sheean et al. [19] speculate, may be due to impaired drive to the primary motor cortex – not due to a lack of motivation.

Physical fatigue often occurs in diverse conditions such as Parkinsonism [20], post-polio syndrome, and in immune-mediated polyneuropathy, where fatigue has been related to anxiety, depression, functional disability and poor quality of life [21]. In Guillain-Barré syndrome, it is rarely disabling [22], though endurance intolerance may persist for years. Investigation of fatigue in these disorders has not yielded a consistent, definable central mechanism.

**Chronic Fatigue Syndrome**

In chronic fatigue syndrome (CFS), fatigue dominates the many disabling symptoms variably present. But if ‘fatigue is only pathological if it is disabling ...’ [12], it is ‘pathological’ in all sufferers from CFS, including an important subgroup whose complaints recover within a year. The syndrome, clinically defined, is characterized by severe disabling fatigue and prominently features subjective impairments in concentration, short-term memory and sleep as well as musculoskeletal pain. Eighteen percent of patients in the Centers for Disease Control and Prevention (CDCP) Report [13] were found to have a pre-

### Table 1. Centers for Disease Control and Prevention’s diagnostic criteria for CFS

<table>
<thead>
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<th>Major criteria (both required)</th>
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<td>– Debilitating fatigue reducing activity to less than 50% of the patient’s premorbid activity for at least 6 months (in adolescents usually reduced to 3 months)</td>
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<td>– Symptoms not explained by other medical or chronic psychiatric illness. The presence of non-psychotic depression does not preclude the diagnosis of CFS</td>
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<td>Symptom criteria (four required)</td>
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<td>– Sore throat</td>
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<td>– Painful cervical or axillary lymphadenopathy</td>
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<td>– Muscle discomfort or pain</td>
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<td>– Prolonged generalized fatigue after usual levels of activity</td>
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<td>– Headaches</td>
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<td>– Arthralgias (without swelling or redness)</td>
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<td>– Neuropsychological disorders, e.g. forgetfulness &amp; lack of concentration</td>
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<td>– Sleep disturbance (unrefreshing sleep)</td>
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1 Adapted from Fukuda et al. [13].
existing medical condition that plausibly accounted for
their chronic fatiguing illness. Diagnosis is by exclusion,
since no pathognomonic signs or diagnostic tests have
been validated in scientific studies; moreover, no consist-
tently effective treatments exist. There is no convincing
evidence to demonstrate persisting viral infection as a
general cause. Patients show a high incidence (~60%) of
depression, emotional symptoms and low self-esteem, al-
though many assert that CFS is not merely a masked form
of depression or a somatoform disorder. Acute post-viral
fatigue syndromes are common in adolescence, but it is
unclear why they become chronic in some young people
[11]. Longitudinal studies show that some persons affect-
ed by CFS improve, but many remain functionally im-
paired for several years.

Fatigue is usually accompanied by other symptoms,
many characteristically psychogenic (table 1) [23]. Wes-
sely and Powell [24] prospectively studied 47 patients
with unexplained chronic post-viral fatigue (CFS) and
compared them with control patients with neuromuscu-
lar and affective disorders. Using criteria that excluded
fatigue itself as a symptom, 72% of the CFS patients were
classed as ‘psychiatric disorder’ compared with 36% of
the neuromuscular group. Mental fatigue and fatigability
was equally common in CFS and depressed patients, but
only occurred in those neuromuscular patients who were
also classed as psychiatric disorder: ‘Overall, the CFS pa-
tients more closely resembled the depressed than the neu-
romuscular patients.’

Medicalized Labels

Doctors sometimes reject fatigue as a symptom of neu-
rosis, for fear of implying it is not genuine. This arises
mainly in the absence of a robust, verifiable definition
and because assessment is subjective. Fatigue can easily
be exaggerated by patients but also by caring profession-
als, whose zealous attentions iatrogenically can induce or
worsen the symptoms [25]. Epidemics and ill-founded
melodramatic nomenclature (e.g., ME) aggravate the
confusion.

Understanding the symptom and hence its place in an
acceptable medical taxonomy is hindered by inconsisten-
ty of definition, methodology and the characteristics of
patients [26]:
• the use by researchers of heterogeneous study
groups,
• the use of study groups selected using different defini-
tions of CFS, and
• the invalid comparisons of contradictory research
findings stemming from the above.

Proponents of uncritical diagnostic labels [27], not
content with their all-embracing ‘diagnostic’ criteria, add
a lengthy footnote of no less than 14 ‘co-morbid entities:
fibromyalgia syndrome, myofascial pain syndrome, tem-
poromandibular joint syndrome, irritable bowel syn-
drome, interstitial cystitis, irritable bladder syndrome,
Raynaud’s phenomenon,…’.

To make sure nobody with fatigue is denied a medical-
ized label, they continue: ‘If the patient has unexplained
prolonged fatigue (6 months or more) but has insufficient
symptoms to meet the criteria for ME/CFS, it should be
classified as idiopathic chronic fatigue.’

Fowler et al.’s [28] paediatric study similarly con-
cludes: ‘Children and adolescents who do not fulfil the
current narrow definition of CFS but do suffer from dis-
abling fatigue show comparable and substantial impair-
ment. In primary care settings, a broader definition of
disabling fatigue [sic] would improve the identification
of impaired children and adolescents who require sup-
port.’

Physiology; Peripheral Fatigue

‘Can chronic fatigue be explained physiologically?’, is
a pertinent question in the absence of a demonstrable
pathogenesis.

Measuring anxiety-related physiological and psycho-
logical reactions to ordinary activity and exercise, CFS
patients and healthy sedentary controls were assessed be-
fore, during and after an incremental exercise test on a
motorized treadmill [29]. Patients with CFS were more
fatigued and sleep disturbed than were the controls and
they noted greater effort during the exercise test. No sta-
tistically significant differences were found in either
heart rate or galvanic skin resistance during a normal day
and before, during and after the exercise test.

Muscle tiredness (‘peripheral fatigue’) is distin-
guished arbitrarily from the more general weariness,
lassitude, or anergia (‘central fatigue’: see above). Muscle
fatigue is frequently defined as a temporary loss in force-
or torque-generating ability because of recent, repetitive
muscle contraction. The development results from the
failure of several processes, including motor (muscle)
unit recruitment and firing rate, chemical transmission
across the neuromuscular junction, propagation of the
action potential along the muscle membrane and tu-
bules, calcium ion (Ca2+) release from the sarcoplasmic
Central Fatigue: Aetiological Considerations

We have shown that diseases of the central nervous system fail to provide a general or specific mechanism for concepts of central fatigue. The factors associated in the literature with CFS might lend understanding to this phenomenon. They include: genetic factors, brain abnormalities (an underactive hypothalamo-pituitary-adrenal axis), deficiencies in cortisol levels or high levels of serotonin, trace element deficiencies, a hyper-reactive immune system, many viral or other infectious agents (such as Epstein-Barr virus), psychiatric or emotional disorders. But the main evidence for such associations has come from retrospective case-control studies, which are subject to many inconsistencies and ascertainment bias [31].

Most investigations show associations, but no specific causal agent(s) that account for patients’ symptoms. Equally, although graded exercises and cognitive behavioural treatments help some sufferers, no generally adequate or curative therapy exists [32].

It is fascinating that with the massive psychological ‘shell shock’ of the First World War traumata, ‘railway fatigue’ disappeared: an interesting hint that biosocial preoccupations can determine the expression of human symptoms. In the aftermath of the ‘September 11’ terrorist attack, the incidence of fatigue syndromes strikingly diminished: prolonged fatigue: 5,450 vs. 1,530/100,000, p = 0. 014 [33]. The causes of this effect are unknown but suggest that perception or manifestation of fatigue can be modified by acute psychological and physiological diversion and adaptations.

Conclusion

In a vast literature, most consider chronic fatigue as a non-specific result of diverse aetiologies. However, there is much inconsistency of definition, methodology and the characteristics of patients between different publications. Little attempt has been made to dissect cause from association or effect(s) in the positive laboratory findings. Many uncertainties have fuelled controversy, polarizing opinions. Patients who meet CFS definitions do not substantially differ by demographic characteristics, symptoms and other illness features from those who fail to satisfy the definition (CDCP). The 1996 Oxford Textbook of Medicine summarized the dilemma: ‘The nature, pathology, and aetiology of this syndrome remain controversial, so the purely descriptive term chronic fatigue syndrome is generally preferred.’

The CDCP report [13] asserts: ‘The central issue in chronic fatigue syndrome research is whether the chronic fatigue syndrome or any subset of it is a pathologically discrete entity, as opposed to a debilitating but nonspecific condition shared by many different entities.’

Few would disagree. We are left with a complaint (symptom), sometimes debilitating, whose basis lies in constitutional factors, the clinical onset precipitated by physical or psychogenic illness or by no identifiable precedent, the course determined by individual resilience and by the social and family reactions to the symptoms. By constitutional is implied the inherent resilience to stresses both organic and emotional; and the ability to succumb to, or withstand such stresses, with consequently restricted or unrestricted work, social function and quality of life.

If adopted without adequate cause, the lifestyle of a chronic fatigue invalid is a grave misfortune for the patient, but also for its reflection on current social attitudes prone to encourage such states. It is not surprising that profound scepticism of this type of illness prevails in certain observers, as the following quotation from Nemesis (Ivan Illich, 1976) illustrates: [On Western Medicine as a mechanism for social control] ‘It serves to legitimise social arrangements into which many people do not fit. It labels the handicapped as unfit, and breeds ever new categories of patients. People who are angered, sickened and impaired by their industrial labour and leisure can escape only into a life under medical supervision and are thereby seduced or disqualified from political struggle for a healthier world.’

The portentous diagnostic labels given to these patients foster rather than alleviate illness. It is possible that
biological factors deriving from a primary illness or incident initiate the process. Whereas most recover without sequelae, in certain subjects the symptoms and disabilities persist and are often discrepant with the initial illness or injury. In this group, the patients’ behaviour may reflect a desire to attain the sick role for secondary gain. If society eliminated the stigma of psychological illness, and opposed exaggeration and simulation of illness, then such chronic disability with ‘retreat into illness’ might disappear [34]. To what extent some patients retreat into a fatigue illness by virtue of intolerable social stresses remains uncertain. The overzealous prescription of diagnoses, medically enforced rest and inactivity, continue to perpetuate symptoms and hinder recovery. Until new, reproducible criteria emerge, we have to agree with the CDCP report that chronic fatigue is a debilitating but non-specific condition shared by many different entities. However, it is neither a valid medical diagnosis nor a verifiable one.

References

26 Report of the National Task Force on Chronic Fatigue Syndrome (CFS), Post-Viral Fatigue Syndrome (PVFS) and Myalgic Encephalomyelitis (ME). Westcare, Bristol, supported by UK Department of Health, 1994.