Chapter 1
What is Chronic Fatigue Syndrome?

Definition and Diagnostic Criteria

Historically, many chronic illnesses have been difficult to define. Specific causative agents are often unknown and diagnostic laboratory tests often have poor sensitivity and specificity (Holmes et al., 1988; Holmes, 1991). Hence, case definitions have been developed through the consensus of expert committees for such illnesses as rheumatoid arthritis, systemic lupus erythematosus and various psychiatric illnesses (Holmes, 1991).

Owing to the unknown aetiology of the illness, specific definition and diagnostic criteria for chronic fatigue syndrome (CFS) were essential to increase understanding, to aid study of the illness and to determine subgroups (Holmes, 1991). Laboratory tests in CFS have also been shown to contribute little to assessment, diagnosis and treatment because of insufficient sensitivity and explicitness (Vercoulen et al., 1994; Bates et al., 1995). Fulfilment of specific criteria would also ensure that other diagnoses such as fibromyalagia were not missed (Goldenberg et al., 1986).

The illness was originally defined in 1988 by a group of American clinicians and researchers working with CFS who met at the Center for Disease Control (CDC) in Atlanta, Georgia, USA (Holmes et al., 1988). Prior to the publication of this definition the illness in the USA had been known as chronic Epstein–Barr virus syndrome. However, doubt had been cast on the relationship between Epstein–Barr and the development of a fatigue state (Buchwald et al., 1987). A new name was therefore proposed, that of CFS (Holmes et al., 1988). CFS described the most noticeable characteristic of the syndrome without implying a causal relationship. As the syndrome had no diagnostic test, the working definition proposed was based on signs and symptoms only (see Figure 1.1). To be defined as CFS a case had to fulfil major criteria 1 and 2, and a certain number of minor criteria: six or more of the 11 symptom criteria and two or more of the three physical criteria; or eight or more of the 11 symptom criteria (Holmes et al., 1988) as cited in Figure 1.1.

MAJOR CRITERIA

1. New onset of persistent or relapsing, debilitating fatigue or easy fatigability in a person who has no previous history of similar symptoms, that 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 history, physical examination and appropriate laboratory findings. These include: malignancy, autoimmune disease; localized infection; chronic or subacute bacterial disease; fungal disease and parasitic disease; chronic psychiatric disease; chronic inflammatory disease; neuromuscular disease; endocrine disease; drug dependency or abuse; side effects of a chronic medication or other toxic agent; or other known or defined pulmonary, cardiac, gastrointestinal, hepatic, renal or haematological disease.

If any results of tests are abnormal the physician should search for other conditions that may cause such a result. If no such conditions are detected by reasonable evaluation, the criterion is satisfied.

MINOR CRITERIA

Symptom Criteria

To fulfil a symptom criteria, a symptom must have begun at or after the time of onset of increased fatigability, and must have persisted, or recurred, over a period of at least six months. Symptoms include:

1. Mild fever
2. Sore throat
3. Painful lymph nodes in the anterior, or posterior cervical, or axillary distribution
4. Unexplained generalized muscle weakness
5. Muscle discomfort or myalgia
6. Prolonged (24 hours or greater) generalized fatigue after levels of exercise that would have been easily tolerated in the patient's premorbid state
7. Generalized headaches
8. Migratory arthralgia without joint swelling or redness
9. Neuropsychologic complaints
10. Sleep disturbance (hypersomnia or insomnia)
11. Description of the main symptom complex as initially developing over a few hours or days

Physical Criteria

Physical criteria must be documented by a physician on at least two occasions, at least 1 month apart.

1. Low grade fever
2. Nonexudative pharyngitis
3. Palpable or tender anterior or posterior cervical or axillary lymph nodes

Source: Holmes et al. (1988)

Figure 1.1 1988 CDC criteria for CFS.

The definition became known as the 1988 CDC criteria. However, these proved difficult to use in practice (Kormaroff and Geiger, 1989). It was found that the definition was frequently modified owing to difficulty in interpreting the criteria and compliance with them (Straus, 1992). The inconsistency in interpretation and application of the CDC definition was confirmed by Schluederberg and colleagues (1992). An Australian definition published by Lloyd and colleagues (1988) was also reported to be unsatisfactory in practice and was not widely accepted (Sharpe et al., 1991).

In an attempt to resolve difficulties encountered in using the 1988 CDC criteria (Holmes et al., 1988), a group of UK clinicians and scientists who were involved in CFS research met in Oxford, UK, to redefine CFS (Sharpe et al., 1991). It was agreed that CFS was the best name, as it was descriptive and free from unproven aetiological implications. The main differences between the definitions were the statement that illness should not be lifelong, and certain exclusions of schizophrenia, manic depressive illness, substance abuse, eating disorder or organic brain disorder were cited. In addition, a subtype of CFS was defined and named post infectious fatigue syndrome (PIFS) (Sharpe et al., 1991). PIFS was defined as fatigue following an infection, or associated with a current infection and the infection should be corroborated by laboratory evidence. However, this definition did not gain wide recognition.

The 1988 CDC criteria were also criticized for not explicitly defining certain terms and not specifying the duration and quality of bedrest and the rigour of neurologic and psychiatric evaluations (Armon and Kurland, 1991). As exclusion of other illness was a major criterion of CFS, in practice confusion centred on the role of depression (Bell, 1992). The UK definition (Sharpe et al., 1991) stated that depressive illness, anxiety and hyperventilation syndrome were not necessarily reasons for exclusion.

An international group of clinicians, scientists and researchers therefore met at the CDC to propose a conceptual framework to enable an integrated and comprehensive approach to the study of CFS (Fukuda et al., 1994). This definition has become the most accepted. It suggests three subdivisions: CFS, post viral fatigue syndrome and idiopathic chronic fatigue. All the case definitions (Holmes et al., 1988; Lloyd et al., 1988; Sharpe et al., 1991; Fukuda et al., 1994) require considerable morbidity from new fatigue in excess of six months with all other recognized causes of fatigue having been excluded by history, observation and clinical assessment. To comply with the 1994 CDC criteria the patient must fulfil both major points, 1 and 2, and present with four or more of the symptoms listed in point 3 shown in Figure 1.2 (Fukuda et al., 1994, pp. 954–956).

(1) New onset of self-reported persistent or relapsing, debilitating fatigue in a person who has no previous history of similar symptoms, that has lasted for six months or longer, is disabling and affects physical and mental functioning and:
   (a) is characterized by fatigue as the principal symptom;
   (b) is of new or definite onset (has not been lifelong);
   (c) is not the result of ongoing exertion;
   (d) is not substantially alleviated by rest;
   (e) results in substantial reduction in previous levels of occupation, educational, social or personal activities.

(2) Other clinical conditions that may produce similar symptoms, including pre-existing psychiatric diseases, must be excluded by thorough evaluation, based on history, physical examination and appropriate laboratory findings. These conditions will include:
   (a) any active medical condition;
   (b) any previously diagnosed medical condition whose continued activity may explain the illness, such as previously treated malignancies and unresolved cases of hepatitis B or C infection;
   (c) any past or current diagnosis of major depressive disorder, including bipolar affective disorder, schizophrenia, delusional disorders, dementia, anorexia nervosa or bulimia nervosa;
   (d) alcohol or substance abuse within two years;
   (e) severe obesity.

(3) Four or more of the following symptoms must be concurrently present for six or more months:
   (a) impaired concentration or memory;
   (b) sore throat;
   (c) tender cervical or axillary lymph nodes;
   (d) muscle pain;
   (e) multi-joint pain without joint swelling or redness;
   (f) headaches of a new type, pattern or severity;
   (g) unrefreshing sleep;
   (h) post-exertional malaise lasting more than 24 hours.

To meet the criteria for post viral fatigue syndrome (PVFS) patients must:

(1) fulfil the criteria for CFS as defined above;
(2) have definite evidence of infection at onset or presentation (a patient's self-report is unlikely to be sufficiently reliable) and should fulfil the following criteria:
   (a) the syndrome is present for a minimum of six months after onset of infection;
   (b) the infection has been corroborated by laboratory evidence.

If the criteria for CFS or PVFS are not met, the fatigue is lifelong and no other cause for the fatigue is identified, a classification of *idiopathic chronic fatigue* would be given.

Source: Fukuda et al. (1994)

Figure 1.2 1994 CDC criteria for CFS.

Aetiology

There is no one theory on the actual cause of CFS. Currently it is thought that different causes or triggers start the illness but result in the same outcome of CFS (Wessely et al., 1989; Surawy et al., 1995). Many researchers have explored a number of possible causative agents, which include:

- infection;
- central nervous system abnormalities;
- chronic immune activation;
- neuromuscular factors;
- psychiatric factors.

Infection

Patients frequently cite an acute 'infection' or 'viral' illness at onset which may not be confirmed on laboratory testing (Lloyd et al., 1990a; Wessely et al., 1995). They often state that their chronic illness 'all started with that virus that never went away' (Kormaroff and Buchwald, 1998, p. 3). Two primary care studies have been carried out in the UK with the aim of determining a relationship between viral illness and the onset of chronic fatigue six months later (Cope et al., 1994; Wessely et al., 1995). In the large cohort study carried out by Wessely and colleagues (1995) they were unable to show any role for common viral infections as aetiological factors. In contrast, Cope and colleagues (1994) found that, at six months following GP-reported acute viral infections, 17.5% of patients remained chronically fatigued.

In the 1980s in the UK, persistent enteroviral infection, in particular Coxsackie B viruses, were implicated in CFS (Calder et al., 1987; Dowsett et al., 1990), and the VP-1 antigen was reported as a possible diagnostic marker (Yousef et al., 1988). However, later investigation did not confirm these findings (Halpin and Wessely, 1989; Lynch and Seth, 1989; Gow et al., 1994; Joyce and Wessely, 1996). In the USA, infective mononucleosis (Epstein–Barr virus) was suggested as a causative factor (Holmes et al., 1988). Doubt was cast on the conclusive evidence of Epstein–Barr virus as the prime cause of CFS, and the possible value of Epstein–Barr virus antibody testing as a diagnostic marker (Kormaroff and Geiger, 1988) following investigation in a general medical practice (Buchwald et al., 1987) and university health centre (Matthews et al., 1991). However, a more recent study in the UK elucidated some evidence of the probable existence of a fatigue syndrome following glandular fever, although not necessarily fulfilling the criteria for CFS (White et al., 1995).

Post-infectious fatigue has been noted after brucellosis, influenza, Epstein–Barr virus, Lyme disease and enterovirus (Imboden et al., 1961; White et al., 1995; Salit, 1997). However, the persistence of such viruses has been shown not to play a part in the pathogenesis of CFS (Gow et al., 1994; Swanink et al., 1995) and to date no evidence of a single infecting agent has been found (Salit, 1997). Viral infection in the community is common though, and the possibility of chance associations between viral infection and the onset of fatigue cannot be excluded (Wessely, 1995b).

Neuromuscular Factors

Neurophysiological explanations have been explored, as most patients complain of profound fatigue and myalgia after exertion, predominantly affecting the muscles (Bearn and Wessely, 1994). Mitochondrial abnormalities have been reported (Behan et al., 1991), and a greater subjective sensation of fatigue and a difficulty in reaching maximal effort has been shown in patients with CFS (Riley et al., 1990; Lloyd et al., 1991). However, this work excluded a simple neuromuscular problem as a credible explanation for CFS (David et al., 1988) and started to pose questions about higher cortical mechanisms (above the level of the motor cortex) and the connection between motor control and feedback (Lloyd et al., 1991).

Central Nervous System

Patients with CFS often complain of symptoms that suggest central nervous system (CNS) involvement. These include cognitive symptoms such as difficulty with concentration, attention and memory, and other symptoms such as photophobia, paresthesia, vertigo and imbalance and headache (Kormaroff and Buchwald, 1998).

Evidence now suggests that changes in the neurobiological mechanisms underlying the stress response at, or above, the level of the hypothalamus, in particular the hypothalamic–pituitary–adrenal axis (HPA), may be relevant to the pathophysiology of CFS (Demitrack et al., 1991; Cleare et al., 1995). Stress-induced activation of the HPA involves activation of 5-hydroxytryptamine (5-HT) neurones (Bearn and Wessely, 1994) and resultant neuroendocrine dysfunction can cause hypocortisolism and upregulation of 5-HT receptors in the hypothalamus (Demitrack et al., 1991; Cleare et al., 1995). As the HPA strongly influences the autonomic nervous system, changes to this function could induce signs of physiological and behavioural arousal, including sympathetic nervous system activation and hyper-responsiveness to sensory stimuli (Demitrack et al., 1991). This may be an explanation as to why patients complain of such diverse symptoms as:

- mood changes;
- nausea;
- dizziness;
- tinnitus;
- temperature control problems;
- sleep disturbance;
- anxiety;
- breathing dysfunction.

The 5-HT neurones are involved in particular with the control of sleep, appetite and mood (Cleare et al., 1995). Different and separable effects on the HPA axis and 5-HT function have been observed in CFS and depression (Cleare et al., 1995). This is an important observation, as some observers have doubted that there is any biological basis for CFS, and have postulated that it represents some form of depression, many patients being told 'it's all in your head' or 'you're just depressed' (Kormoroff and Buchwald, 1998). Interestingly, comparable HPA changes have been found in CFS and fibromyalgia, possibly indicating some degree of commonality between the syndromes (Moldofsky, 1995). Buchwald and Garrity (1994) found that demographic and clinical factors, and health beliefs and locus of control did not clearly distinguish patients with CFS and fibromyalgia.

However, a recent study failed to replicate the HPA changes in CFS patients (Young et al., 1998). A possible reason for failure to replicate previous findings was the type of patient group and their duration of symptoms. In the study by Young and colleagues (1998) patients were referred from primary care with a mean duration of symptoms of 2.5 years whereas, in previous studies, patients were referred from secondary and tertiary care (Demitrack et al., 1991; Cleare et al., 1995), and had a mean duration of symptoms of 7.2 years (Demitrack et al., 1991). This may indicate that HPA involvement is dependent on the chronicity of the illness and is therefore a consequence of the illness rather than a cause.

Some specific diagnostic studies of the CNS have found abnormalities in patients with CFS using techniques such as magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT) (Kormaroff and Buchwald, 1998) and sensory and cognitive event-related potentials (ERPs) (Prasher et al., 1990). As yet, though, there has been no identifiable pattern to the abnormalities seen through testing, for any of these to be considered as a diagnostic test. There has also been little consistency in the abnormal findings reported between the tests (Cope and David, 1996). In addition, the neuroimaging abnormalities have not yet been correlated with clinical findings in CFS (Bearn and Wessely, 1994; Cope and David,

1996), and therefore the role of CNS abnormalities seen in the pathophysiology of CFS is yet to be determined (Kormaroff and Buchwald, 1998).

The role of the CNS has been further explored through a number of studies on sleep disorder. Most patients with CFS complain of difficulty getting off to sleep, sleeping lightly and being unrefreshed on waking (Moldofsky, 1995). Morriss and colleagues (1993) postulated that the sleep disorder associated with the illness could be important in the aetiology of CFS, as the effects of sleep loss on performance of patients with sleep disorders were similar to the complaints of patients with CFS which include:

- increased subjective effort on exertion and slower subsequent recovery;
- reduced vigilance;
  attention span;
  cognitive performance.

(Morriss et al., 1993)

However, in a later study (Morriss et al., 1997) the group could find little evidence that disrupted sleep is associated with the onset of CFS. Instead, waking at night was often associated with pain and feeling hot or cold. They proposed that disrupted sleep was therefore:

> ...linked to physiological and psychological mechanisms involved with the production of myalgia or abnormal sensitivity to pain or temperature disturbance rather than physical or mental fatigue. (p. 605)

Sharpley and colleagues (1997) confirmed this conclusion by stating that:

> ...sleep abnormalities are merely an epiphenomenon. If patients have sought to overcome their fatigue by spending longer in bed at night and sleeping during the day, the observed sleep inefficiency could be simply a consequence of this behaviour. (p. 595)

Therefore abnormalities of sleep do not appear to be of major importance in the aetiology of CFS, but rather a consequence of the illness which can worsen over time (Morriss et al., 1997; Sharpley et al., 1997).

Further evidence as to the involvement of CNS dysfunction in CFS has been highlighted by the studies that have considered the cognitive impairment expressed by the majority of patients (Marshall et al., 1997; Kormaroff and Buchwald, 1998). DeLuca and colleagues (1993) concluded that selective impairment in information processing, in partic-

ular auditory material, could be the root of other cognitive complaints made by patients with CFS and confirmed this finding in a later study (DeLuca et al., 1995). It has been postulated that impaired information-processing ability in patients with CFS may be due to changes in cerebral white matter (DeLuca et al., 1995). However, a quantitative summary of the most rigorous MRI studies has shown no significant increase in white-matter lesions in CFS (Cope and David, 1996).

Psychiatric Factors

Joyce et al. (1996) identified that cognitive dysfunction was related to:

> ...reduced attentional capacity which results in impaired performance on effortful tasks requiring planned or self-ordered generation of responses from memory. (p. 495)

They also showed that there was little evidence that the deficits seen in CFS reflected a depressive illness. McDonald and colleagues (McDonald, Cope and David, 1993) also noted that the cognitive impairment found could not be explained by the presence of depression amongst patients with CFS. However the nature of the information-processing deficit is shown to be undistinguished from depression and appears to be a common deficit in both disorders (DeLuca et al., 1995; Marshall et al., 1997). In an effortful cognitive recall task on written information, slight evidence that CFS patients (whether depressed or not) were impaired has been noted (Wearden and Appleby, 1997).

DeLuca and colleagues (1997) subsequently concurred with McDonald and colleagues (1993) that the impaired cognition could not be explained solely by the presence of a psychiatric condition (primarily major depression) and that cognitive dysfunction was not induced by depression. In addition, they found that cognitive functioning was worse in CFS without a co-morbid psychiatric condition (DeLuca et al., 1997). In a later study (Christodoulou et al., 1998), it was also found that cognitive impairment was related to functional disability that could not be explained on the basis of psychiatric factors. These results, although they did not assist in confirming the aetiology of CFS, have implications for treatment. DeLuca and colleagues (1997) suggested that:

> ...patients with CFS with psychiatric complications may benefit more from psychotherapy in conjunction with psychopharmacological interventions. By contrast, patients without psychiatric co-morbidity may benefit more from a psycho-educational approach to symptom management or cognitive rehabilitation. (p. 154)

Marshall and colleagues (1997) suggested that the depression seen in CFS was a reaction to the illness and usually developed well after the onset of CFS and therefore might be considered a 'reactive depression' rather than major depression, thus adding weight to the conclusion that previous psychiatric disorder does not cause CFS but is a consequence of the disorder (Hickie et al., 1990). It would appear that primary major depression does not account for the cognitive difficulties found in CFS patients (Marshall et al., 1997).

Many patients with CFS do not suffer from mood, anxiety or somatization disorders (Kormaroff and Buchwald, 1998). However, one explanation for the possible link between CFS and psychiatric disorder sometimes seen as a consequence of or prior to the illness is that it may be due to some common neurobiological dysfunction rather than misdiagnosed cases of depression and anxiety (Joyce and Wessely, 1996; Cleare, 1997). The estimated prevalence of pre-morbid lifetime total psychiatric disorder in CFS has been put at 24% and major depression at 12.5% (Hickie et al., 1990).

The argument as to whether the cognitive deficits and/or psychiatric factors are due to a psychological consequence or aetiology in CFS is not conclusive. However, evidence of a consistent pattern of neuropsychological impairment is available including slower reaction times and information processing, and poorer performance on complex attentional and memory tasks (Moss-Morris et al., 1996; DeLuca et al., 1997).

Immune Dysfunction

Considerable attention has been given to the possible role of immune dysfunction in CFS (Wessely, 1995a). Various abnormalities have been suggested, but only a few have been consistently reported: elevated levels of immune complexes (IgG levels); increased numbers of CD8+ cytotoxic T cells; and depressed function of natural killer lymphocytes (Bates et al., 1995; Komaroff and Buchwald, 1998). These abnormalities may be evidence of ongoing activation of the immune system in CFS (Bates et al., 1995). However, the theory that a state of immune activation could disrupt neurotransmitter function and result in the symptoms of CFS remains unproven (Bearn and Wessely, 1994; Kormaroff and Buchwald, 1998). It also remains to be seen whether the immune abnormalities observed distinguish patients with CFS from other illnesses that could mimic CFS clinically, such as systemic lupus erythematosus (Buchwald and Kormaroff, 1991).

In conclusion, despite all the studies discussed, as yet there is no definitive cause for CFS. All reports appear to point towards CNS mechanisms but it is unclear whether they are primary or secondary to the illness and decreased physical activity. All agree that well-designed rigorous studies

with appropriate statistical power are required. Current theory appears to suggest that the cause is multi-factorial, and that a combination of infective, physiological and psychological factors that creates dysfunction within the CNS is involved (Wessely, 1995b; Salit, 1997).

Clinical Features and Presentation

In 1994 Leitch described CFS as 'a complex amalgam of social, cultural, psychological and somatic factors' (p. 501). He makes the point that these factors and their interactions need to be addressed if a satisfactory outcome is to be possible (Leitch, 1994).

Clinical Features

From clinical experience, the commonest presentation seems to occur as a result of chronic stressors in a vulnerable individual (Cox and Findley, 1998). The other primary contributing factor is the report of a 'flu-like' illness at the onset (Salit, 1997; Kormaroff and Buchwald, 1998). The main complaint is persistent fatigue that differs from normal tiredness. The extreme fatigue affects both mental and physical capacity, reducing a person's activity ability substantially below his/her previous level of functioning (Joyce and Wessely, 1996; Cox, 1998). It is accompanied by a range of other unpleasant symptoms, such as:

- muscle and/ or joint pain;
- daily headache;
- recurrent sore throats;
- fluctuations in mood;
- intolerance of alcohol;
- cognitive processing difficulties which result in poor concentration and memory problems;
- autonomic changes such as temperature control problems, night sweats, digestive changes and palpitations (Hickie et al., 1995; Kormaroff and Buchwald, 1998; Cox, 1998).

A 'triangle of pain' from the posterior base of the skull to below the scapulae is often described, predominantly affecting the upper part of the trapezius (Cox, 1998).

Problems with sleep are common, and include sleeping longer than normal often at the beginning of the illness, and having difficulty getting off to sleep and waking frequently as the illness progresses (Morriss et al., 1993; Moldofsky, 1995). Whatever the problem, the sleep is seldom refreshing (Sharpe et al., 1997). The overall symptoms vary in degree in

each individual (Behan and Behan, 1988) and are exacerbated by minimal exertion, unexplained by conventional biomedical diagnosis (Sharpe et al., 1997).

The degree of dysfunction can vary from mild to very severe (Behan and Behan, 1988). Mild is the level where patients are still mobile for short distances, able to carry out some outdoor activities and continue to work part time. Very severe is assessed to be when the patient is totally dependent on the support of others and predominantly in bed (Cox and Findley, 1998). In more severely affected individuals late-stage anxiety is often seen (Cox, 1998).

Presentation

Certain factors are thought to predispose, precipitate (trigger) and perpetuate the illness and what precipitates or causes CFS may not necessarily perpetuate it (Surawy et al., 1995). The perpetuators are often the effects of inactivity, inconsistent activity, illness beliefs and fears about symptoms and symptom focusing (Joyce and Wessely, 1996; Sharpe et al., 1996).

From experience the predisposing factors to the illness appear to be prolonged high striving and achievement, i.e. the person has a tendency to overwork, sets high standards and tends not to stop for illness (Surawy et al., 1995; Cox, 1999a). Patients will describe their pre-morbid lifestyle as being characterized by perfectionism, and high standards for work performance, responsibility and personal conduct, often placing great value on the opinion of others (Surawy et al., 1995).

Prior to the onset of CFS a person usually experiences a combination of psychosocial stress and an acute 'flu-like' illness (Sharpe et al., 1997; Kormaroff and Buchwald, 1998). The main precipitators or triggers that have been identified are a combination of:

- viral infections;
- significant internal and external stressors;
- overwork.

(Surawy et al., 1995)

The significant stressors will be those that place severe demands on the person or lead to depletion of their personal resources or both. A minor illness may then act as the final precipitating event or as a 'last straw' that tips the person into ill health (Surawy et al., 1995; Cox and Findley, 1998). For most patients it appears to be a combination of factors.

In the same way as the illness will have been triggered by certain factors there will be perpetuators of the illness. These are often similar to the precipitators, usually stress and recurrent infections, and the patterns that can develop in response to the symptoms (Joyce and Wessely, 1996; Cox, 1999a).

Therefore, once a state of fatigue is established, cognitive, behavioural, emotional, physiological and social factors may act to perpetuate it, such as:

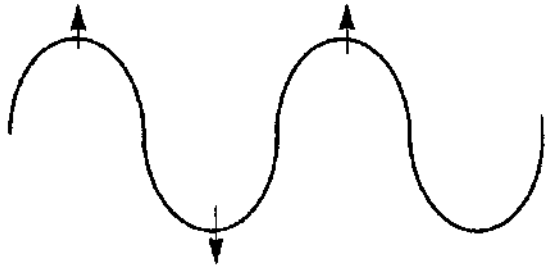
- unhelpful beliefs;
- ineffective coping behaviour;
- negative mood states;
- social problems;
- pathophysiological processes.

(Surawy et al., 1995; Sharpe et al., 1996)

A vicious cycle then ensues, which traps the patients in chronic illness.

Inconsistent activity, and illness beliefs and fears about symptoms can fuel the illness (Joyce and Wessely, 1996; Sharpe et al., 1997). A person with CFS will not recover if he/she only has prolonged rest or pushes him/herself to the absolute limit (Joyce and Wessely, 1996). Rest can bring about short-term relief but in the longer term reduces activity tolerance (Cox and Findley, 1994). Conversely, strenuous activity following prolonged periods of rest has been shown to increase symptoms that perpetuate and reinforce activity avoidance behaviour (Butler et al., 1991). From this fluctuation between bursts of activity and prolonged rest, the pattern of activity has been described as the 'see-saw' effect, or peaks and troughs (Joyce and Wessely, 1996; Cox, 1999a).

The peaks of activity usually occur when patients with CFS feel well. They consequently tend to push themselves (peak) in an attempt to regain 'normal' function, and often go beyond their current fitness capacity so that they then have an excessive increase in symptomst. As a result of the increase in symptoms they take prolonged rest (trough) and so the cycle recurs (Sharpe et al., 1997; Cox, 1999a). This pattern happens on a daily and weekly basis, patients often carrying out most activity in the morning, then resting or sleeping each afternoon. Figure 1.3 describes this process diagrammatically.

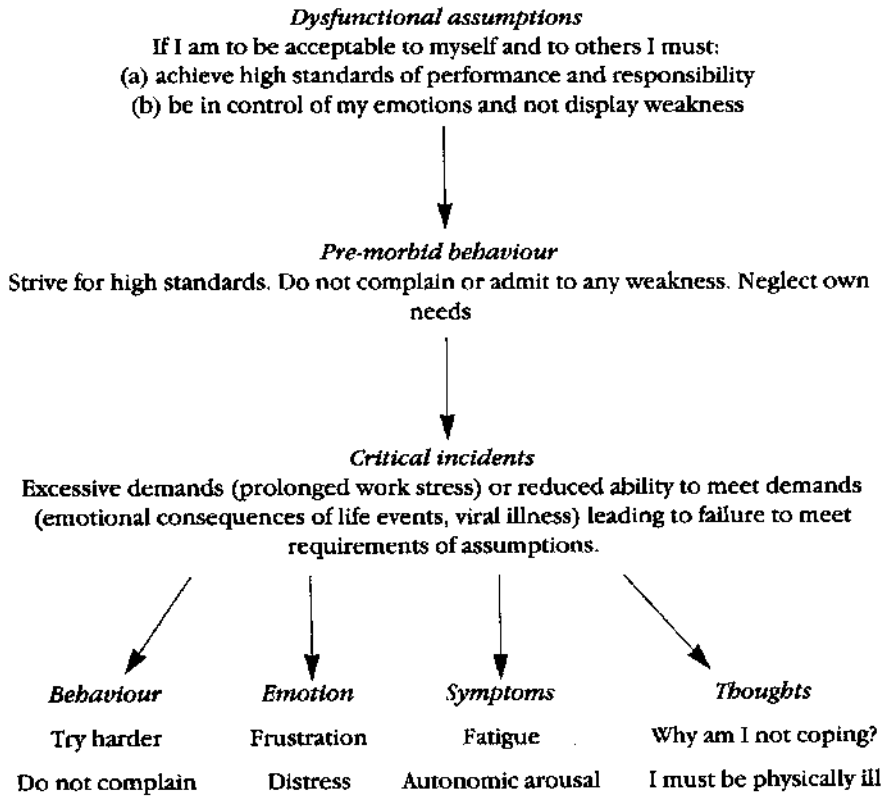


Not only occurs on a daily basis in response to symptoms but also weekly and monthly

Figure 1.3 The pattern of peaks and troughs of ability seen in CFS.

In addition, patients find that, owing to the fluctuations in symptoms, they may have two to three good days (peak) followed by two to three bad days (trough) (Cox, 1999a). Delayed fatigue and myalgia usually occur between 24 and 48 hours after any exertion in excess of the patient's current fitness level (Joyce and Wessely, 1996).

Following the observation of the impact on the CNS a cognitive model has been used when describing the precipitation and perpetuation of CFS (Surawy et al., 1995; Sharpe et al., 1996). Figure 1.4 shows the cycle as described by Surawy and colleagues (1995). In the absence of precise aetiology, using this model it is possible to see why cognitive approaches to the treatment of this illness have been used. The cognitive model constitutes a range of pragmatic approaches that effect change in an individual's ability and quality of life (Surawy et al., 1995; Sharpe et al., 1996; Deale et al., 1997).



Source: Surawy et al. (1995)

Figure 1.4 Theoretical cognitive model of actiology and consequence of CFS.

It is from this model, combined with personal clinical experience and published evidence of effect, that the specific approach utilized by the author was developed, this is explained in detail in Section Four.

The following case vignette aims to illustrate a typical onset, presentation of the illness and consequent impact on an individual's life.

Case Vignette 1

Jane (aged 44) described the onset of her illness as starting five years prior to attendance. The onset followed a simple operation at her local hospital for removal of a tooth abscess. She stated that at the time she was under a lot of personal stress and had financial worries. Her mother had died in the previous year. On attendance at the occupational therapy session, she described her current symptoms as right-sided weakness and pain, sudden draining of energy, headache, generalized fatigue and a dry mouth. She was currently taking 50 mg of amitriptyline two hours prior to going to bed to assist with sleep disturbance. However, she said she still had difficulty getting off to sleep, woke frequently during the night and generally woke each morning feeling unrefreshed.

At the time of the onset of the illness she was working as a music therapist at her local centre for children with learning difficulties. She had stopped work two years ago as a result of the illness. Jane lived alone in her own house and could currently manage all her own personal care activities. However, she was reliant on her family and friends to complete domestic tasks, and was not currently able to socialize for longer than 10 minutes with one person in her own home. She was not able to maintain her normal social activities of attending the local church and visiting family and friends.

Prevalence and Prognosis

Prevalence

Overall, prevalence of CFS in the UK has been suggested to be 150 000 cases, with a 2:1 predominance of females compared with males (Wallace, 1991; Hinds and McCluskey, 1993). Table 1.1 shows the prevalence and prognosis from various studies of chronic fatigue around the world, and more specifically CFS. As can be seen from Table 1.1, more recent studies suggest a 3:1 predominance of females to males (Pawlikowska et al., 1994; Clark et al., 1995; Vercoulen et al., 1996) and the population prevalence of CFS to be between 0.3% and 1.5% (Bates et al., 1993; Pawlikowska et al., 1994; Buchwald et al., 1995; Wessely et al., 1995). In a sample taken from employees in an office building 0.9% met criteria for CFS (Shefer et al., 1997). Prevalence appears to be dependent on the case

Table 1.1 Prevalence and prognosis in studies of CF and CFS

Study	Setting and definition used	Duration of symptoms, age at outset and gender ratio (female: male)	Prevalence per 100 000 (type or definition)	Main outcome measures used	Assessment period	Conclusions
Bates et al., 1993	USA, primary care clinic, urban hospital-based general medicine practice $n = 26$ (CF) CFS $n = 3$ CDC Holmes et al., 1998 $n = 4$ UK, Sharpe et al., 1991 $n = 10$ Lloyd et al., 1990a	Duration > 6 months Mean age = 41.4 (CFS) Ratio 2:1	CDC = 0.3% UK = 0.4% Australia = 1.0% CFS only counts for small fraction of all cases of chronic, debilitating fatigue	Detailed history Physical examination Laboratory testing Psychiatric testing	1 year follow up	All 3 CFS patients remained fatigued Prevalence depends on case definition used
Buchwald et al., 1995	USA, health maintenance organization. $n = 74$ (CF) $n = 3$, CFS CDC Holmes et al., 1988	CFS = 6.1 years CF = 5.5 years Mean age = 41.3 (CFS) 44.9 (CF) Ratio 2:1	CFS = 75 to 267 (0.3%) CF = 1775 to 6321	SCL-90, SF-36, Brief fatigue inventory Symptom questionnaire Laboratory testing and physical examination	12 months 24 months	All 3 CFS patients remained fatigued. CFS and CF had poorer functional status and greater psychological distress than controls

Clark et al., 1995	USA, tertiary care, chronic fatigue clinic, university medical school n = 78, 19 (24%) met CFS 1988 CDC criteria	CF = 5.5 years Mean age = 39.9 Ratio 3:1	None given	Self-report questionnaire	$2^1/_2$ years	32/78 (41%) rated moderate to complete recovery 7/19 (37%) CFS patients recovered Poor outcome associated with older age (>38),longer duration of symptoms (>1.5 years), multiple physical symptoms, lifelong dysthymia
David et al., 1990	UK, primary care 611 general practice attenders, 64 had fatigue of greater than 1 month, 1 had CFS	> 1 week to > 6 months Mean age men = 38.8 women = 33.2 Ratio 2.8:1	None given Fatigue common complaint among general practice attenders and can be severe	Fatigue questionnaire (Wessely, 1989)	Initial only	Prognosis: none given Patients attribute illness to physical, psychological and social stress
Gold et al., 1990	USA, virology clinic n = 26 with at least 9 months of fatigue with physical symptoms and raised EBV titres. n = 6 CFS, 1998 CDC	Duration of CF = 3.5 years Mean age = 34.4 Ratio 1.4:1	None given	Symptom score Patients' assessment of improvement	3 to 21 months, mean, 11.3 months	4/21 complete recovery 8/21 significantly improved CFS 3/5 improved Most patients improve over time

(contd)

Table 1.1 (contd)

Study	Setting and definition used	Duration of symptoms, age at outset and gender ratio (female: male)	Prevalence per 100 000 (type or definition)	Main outcome measures used	Assessment period	Conclusions
Hinds and McCluskey, 1993	Northern Ireland, immunology outpatient clinic $n = 393$, 291 returned	Mean duration 5.22 years Mean age = 33 Ratio 2:1 females to males	None given	Postal questionnaire	Unclear, up to 6 years follow up	54 (18.6%) fully recovered Younger patients and those with a shorter duration of symptoms more likely to recover
Kroenke, et al., 1988	USA, army primary care clinic CF $n = 102$	Mean duration = 3.3 years Mean age range 40–64 Ratio 1.4:1	24% in the clinic population	Symptom of fatigue (2 scales). Changes in medical condition, medications, number of visits and hospitalizations	1 year follow up	29 (28%) with CF improved Older age and greater disability, abnormal ESR and clinic visits associated with poorer outcome
Lloyd et al., 1990	Australia, community CFS $n = 42$ (CDC Holmes, 1988)	Mean duration = 30 months Mean age = 28.6 yrs Ratio 1.3:1, less in community than tertiary care	CFS = 37.1 cases	Interview Psychiatric and medical assessment	None	CFS affects young individuals from all social classes and causes considerable ill health and disability
McDonald, David et al., 1993	UK, primary care attenders	Duration = >1 year Mean age = 32.5	None given	Interview Physical history	1 to 5 months	Prognosis: none given

	CF n = 77 of which CFS = 17 (Sharpe et al., 1991)	Ratio 3:1		and examination data Socio-demographic Fatigue questionnaire Attributions		Identification of persistent fatigue and management in primary care may prevent secondary disabilities seen in CFS
Pawlikowska et al., 1994	UK, 6 primary care practices in southern England CF n = 2798 of which 38 = CFS	Duration = 18% >6 months Mean age not given Ratio 3:1	None given Possible 1%	Fatigue questionnaire GHQ	Community survey	Prognosis: none given General fatigue continuous variable in community
Ridsdale et al., 1993	UK, general practice Fatigue n = 220 of which 59% possible CFS	Duration = > 3 months Mean age = 43 Ratio 1.3:1	None given	Clinical data Laboratory tests Fatigue questionnaire GHQ	2 weeks, 2 and 6 months	Poor prognosis duration of symptoms longer than 6 months and history of anxiety or depression
Sharpe et al., 1992	UK, infectious diseases clinic n = 144 unexplained fatigued (CFS)	Median duration = 25 months Median age = 34 Ratio 1.5:1	None given	Assessment and interview questionnaires on degrees of recovery and functional impairment	6 weeks to 4 years	Functional impairment associated with belief in a viral cause, avoiding alcohol, changing or leaving employment, belonging to a self-help organization and current emotional disorder 13 % fully recovered, 65% were functionally impaired

(contd)

Table 1.1 (contd)

Study	Setting and definition used	Duration of symptoms, age at outset and gender ratio (female: male)	Prevalence per 100 000 (type or definition)	Main outcome measures used	Assessment period	Conclusions
Vercoulen et al., 1996	Holland, hospital clinic CFS n = 246	Mean duration 8.4 years Mean age = 39 Ratio 3:1	None given	Subjective experience Psychological well-being Functional impairment (SIP) Sleep disturbances Avoidance behaviour Neuropsychological functioning Social interactions Sense of control and causal attributions	18 months	3% complete recovery, 17% reported improvement Predictors of improvement were subjective sense of control over symptoms, less fatigue, shorter duration of complaints and a relative absence of physical attributions
Wessely et al., 1995	UK, primary care CF n = 100 CFS n = 12 (CDC, 1994)	Mean duration = 6 months Mean age = 32.7 Ratio 2:1	1.5 % Onset linked to previous fatigue and psychological disorder	Fatigue questionnaire GHQ CFS checklist Psychological assessment MOS short form	6 months' follow up	No evidence to suggest that common viral infections are associated with CFS in primary care

Wilson et al., 1994a	Australia, university hospital referral centre CFS n = 103 (CDC, 1988)	Mean duration = 9.2 years Mean age = 42.2 Ratio 2.5:1	None given	Somatic symptoms Structured interview Functional questionnaire Karnofsky performance index	Follow up mean 3.2 years after initial assessment	6% complete recovery, 63% improved Psychological factors such as illness attitudes and coping are predictors of long-term outcome Strong conviction in a physical disease associated with poor outcome

CFS = chronic fatigue syndrome
CF = chronic fatigue
CDC = Centre for Disease Control.

definition used. With three different CFS definitions (Holmes et al., 1988; Lloyd et al., 1990a; Sharpe et al., 1991) the prevalence ranged from 0.3% to 1% (Bates et al., 1993). In a later study this figure was adjusted to 98 per 100 000 (Buchwald et al., 1995).

One of the problems with many of the studies carried out on prevalence to date is possible selection bias. Almost all are based on tertiary care samples of patients, with patients often making their own diagnosis prior to seeking help (Wessley, 1995a). The more recent UK study in primary care (Pawlikowska et al., 1994) would appear to give the most realistic prevalence figure to date of 1%; however, in the same study only 0.2% thought that they had CFS (ME). Wessely (1995a) has stated that the 'systematic surveys that are now being published are beginning to suggest that CFS represents a substantial but neglected public health problem' (p. 142).

In the general population, chronic fatigue is a common complaint in primary care practice attendees with 18–27% (Kroenke et al., 1988; David et al., 1990; Bates et al., 1993; Pawlikowska et al., 1994) complaining of fatigue. However, only one in 10 of those patients would fulfil the criteria for CFS (Wessely et al., 1995).

The studies that have been completed in primary care do not indicate the higher predominance of professionals often seen in specialist secondary and tertiary referral centres and indicate no effect of sex or social class (Lloyd et al., 1990a; Wessely et al., 1995). The ratio of females to males in primary care also appears to be less than in secondary and tertiary care, with a ratio of 2:1 rather than 3:1 (Lloyd et al., 1990a). Lloyd and colleagues (1990a) conclude that the disorder is relatively common, affecting young adults in an approximately equal sex distribution. The most common time to develop the syndrome is in the peak productive years, with resulting disability persisting for prolonged periods of time.

Differences have been noted between the populations seen in primary and tertiary care (Euba et al., 1996). In particular, women are over represented in hospital samples. Gender could therefore be a weak risk factor for CFS. Overall, men have a worse perception of their health. Hospital cases often report less psychological distress (Euba et al., 1996), despite having more severe levels of fatigue. Self-diagnosis is more common in tertiary centres and a substantial number of patients are referred to specialists who do not fulfil the criteria for CFS (Wilson et al., 1994a). All these differences would need to be taken into consideration when evaluating a hospital CFS population.

Prognosis

Evidence of effective treatments for CFS is limited (Sharpe et al., 1996; Deale et al., 1997; Fulcher and White, 1997) and overall prognosis and recovery rate have been reported as generally extremely poor (Wessely, 1995a).

In 1988, Behan and Behan described the outcome of patients referred to a neurology service as follows:

> Most cases do not improve, give up their work and became permanent invalids, incapacitated by excessive fatigue and myalgia. (p.164)

There is evidence to support such gloomy outcomes. As can be seen from Table 1.1, studies over varying time scales of six months' to three years' follow up have indicated that with no intervention or management only 3–37% were fully recovered (Kroenke et al., 1988; Sharpe et al., 1992; Hinds and McCluskey, 1993; Wessely, 1995a; Vercoulen et al., 1996). However, with active medical care in a specialist CFS clinic 63% of patients were improved at a mean of 3.2 years' follow up, although only 6% had recovered completely (Wilson et al., 1994a). Those with chronic fatigue alone rather than CFS appear to show greater improvement, with 25% reporting resolution of their fatigue at one-year follow up (Buchwald et al., 1995). This may have an implication for the research design used to examine treatment methods and may indicate the fluctuating nature of the illness. Assessment may need to be carried out on a number of occasions to gain a true picture of improvement and recovery rather than just one or two time slots (Ray et al., 1997).

Patients with a subjective sense of control over symptoms, less fatigue, shorter duration of symptoms and an absence of physical attributions are more likely to improve (Sharpe et al., 1992; Vercoulen et al., 1996). In specialist settings poor prognosis appears to be associated with older age (Kroenke et al., 1988), the strength of physical attribution (Wilson et al., 1994a) and current emotional disorder (Euba et al., 1996). Psychological factors such as illness attitudes and coping appear to be predictors of long-term outcome (Wilson et al., 1994a; Vercoulen et al., 1996), in that belief in a physical cause, behavioural disengagement and coping mechanisms may effect recovery. Beliefs about illness could be considered important predictors of behaviour and desire to participate in rehabilitation (Joyce et al., 1997). Longitudinal studies that examine psychobiological relations between psychological distress and coping style, immunological function and the natural course of CFS are needed (Wilson et al., 1994a).