

*Ministry of Defence*

## **Synopsis of Causation**

### **Chronic Fatigue Syndrome**

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## **Disclaimer**

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This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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# 1. Definition

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- 1.1 Chronic fatigue syndrome (CFS) is a significant illness that causes severe disabling physical and mental fatigue exacerbated by minimal exertion, in the absence of any conventional physical or psychological disorder to explain the problem. The term “chronic fatigue syndrome” was conceived relatively recently. However, the symptom complex that it describes has been recognised for over a century, during which time it has been classified under a variety of titles including neurasthenia, Royal Free disease, myalgic encephalomyelitis (ME), and post-viral fatigue syndrome.
- 1.2 CFS is **defined by symptoms and disability** and has **no confirmatory physical signs or characteristic laboratory abnormalities**. A number of case definitions have been proposed. The most widely used definition, developed by Fukuda et al in 1994, outlines both **inclusion** and **exclusion** criteria for the diagnosis of CFS, as follows:<sup>1</sup>
- 1.2.1 **Inclusion criteria:** A case of the chronic fatigue syndrome is defined by the presence of clinically evaluated, unexplained persistent or relapsing chronic fatigue that is of new or definite onset (i.e. not lifelong); is not the result of ongoing exertion; is not substantially alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities; **and**
- 1.2.2 The concurrent occurrence of four or more of the following symptoms, all of which must have persisted or recurred during six or more consecutive months of illness and must not have predated the fatigue:
- Substantial impairment in short-term memory or concentration
  - Sore throat
  - Tender lymph nodes
  - Muscle pain
  - Multi-joint pain without joint swelling or redness
  - Headaches of a new type, pattern, or severity
  - Unrefreshing sleep
  - Post-exertional malaise lasting more than 24 hours
- 1.2.3 **Exclusion criteria:** The following conditions exclude a patient from the diagnosis of CFS:
- Any active medical condition that may explain the presence of chronic fatigue, such as untreated hypothyroidism, sleep apnoea, [narcolepsy](#), and the side effects of medication
  - Any previously diagnosed medical condition whose resolution has not been documented beyond reasonable clinical doubt and whose continued activity may explain the chronic fatiguing illness e.g. previously treated malignancies
  - Any past or current diagnosis of a major depressive disorder with psychotic or melancholic features; bipolar affective disorders; schizophrenia; delusional disorders; dementias; anorexia nervosa; or bulimia nervosa
  - Alcohol or other substance abuse within 2 years prior to the onset of the chronic fatigue and any time afterward

- Severe obesity as defined by a body mass index equal to or greater than 45
- 1.3 In applying the case definition based on the criteria developed by Fukuda et al, ambiguities may arise that contribute to inconsistencies in case identification. A number of standardised and validated instruments involving structured interviews and questionnaires are advocated to improve the assessment of fatigue, disability, and symptoms associated with CFS. It is suggested that the adoption of such methods will improve the precision of case identification and render it more uniform across different sites. These issues are particular germane to researchers but are also of relevance in the clinical setting.<sup>2</sup>
- 1.4 **“Idiopathic chronic fatigue”** is a term used to describe clinically evaluated, unexplained chronic fatigue that fails to meet criteria for the chronic fatigue syndrome.

## 2. Clinical Features

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- 2.1 Studies conducted by the Centers for Disease Control and Prevention in the USA have suggested that the prevalence of CFS may lie in the region of 200 people per 100,000 population. There is evidence that CFS affects all racial and ethnic groups and both sexes, although most surveys support a female preponderance. Past reports of an increased prevalence of CFS amongst white patients have emanated from clinic populations, and it is likely that these results merely reflect a bias attributable to health care access and utilisation. Average age of onset is around 30 years. Adolescents can have CFS with many of the same characteristics as demonstrated in adults. CFS-like illness has been reported in children under 12, although the symptom pattern varies somewhat from that seen in adults and adolescents.<sup>3</sup>
- 2.2 The Fukuda criteria for the diagnosis of CFS have been listed at section 1.2. CFS is a **diagnosis of exclusion**. Thus all other physical and psychiatric bases for the patient's fatigue must be excluded before a diagnosis of CFS is made.
- 2.3 The **history** is useful in eliciting information in a number of areas:<sup>4</sup>
- Symptoms relevant to the Fukuda criteria, including details of fatigue and its relation to exertion, physical symptoms, sleep disturbance, and cognitive problems such as poor concentration and memory
  - Disability and distress illustrating how the patient's life has been changed by the illness
  - The patient's understanding of the illness
  - Coping strategies, especially with regard to rest and activity
  - Employment situation
  - The attitude of family members
- 2.4 The presence of abnormal signs on **physical examination** is not generally considered to be compatible with a diagnosis of CFS. However, muscle wasting and [postural hypotension](#) may become evident in patients with CFS, having arisen as a consequence of inactivity. A **mental state examination** is also vital to exclude alternative diagnoses and to identify comorbid mental health conditions.
- 2.5 When the patient first presents, an appropriate range of screening **investigations** should be carried out to exclude alternative diagnoses. Any pointers to alternative diagnoses that have been elicited from the history and examination may also merit specific investigation in their own right. However, there is **no diagnostic test or pattern of tests** that will serve to **make** a diagnosis of CFS.
- 2.6 Patients may perceive a lack of understanding from others, including health professionals. They may be referred to a variety of specialist clinics or choose to consult alternative practitioners. The struggles of sufferers and professionals to understand the illness may lead to unsatisfactory patient-professional relationships and resentful patients.<sup>5</sup>
- 2.7 There is a significant overlap between CFS and other conditions that are characterised by unexplained health symptoms. It has been reported that a significant proportion of Gulf War veterans who present with unexplained fatigue meet the criteria for CFS.<sup>6</sup>

CFS also shares many of the clinical features of fibromyalgia (notably muscle pain), and so differentiation is sometimes difficult. The majority of patients with fibromyalgia do fulfil the diagnostic Fukuda criteria for CFS but are traditionally characterised as having a chronic pain rather than a chronic fatigue syndrome.

### 3. Aetiology

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- 3.1 The underlying cause of CFS remains unknown. The most useful approach is to consider CFS as a descriptive term for a **type of clinical presentation**, i.e. a [heterogeneous](#) disease whereby a number of mechanisms may manifest with similar symptoms.
- 3.2 Aetiological theories abound, but none is established. The following mechanisms are among the theories that have been put forward as causes of CFS:
- 3.2.1 **Disturbance of the [hypothalamic-pituitary-adrenal \(HPA\) axis](#):** the overall balance of evidence points to reduced [cortisol](#) output in at least some patients, although recent studies have suggested an absence of HPA axis changes during the early stages of the development of CFS. The later-occurring HPA axis changes can be reversed by modifying behavioural features of the condition such as inactivity, deconditioning and sleep disturbance. Thus, it appears likely that the HPA axis disturbance observed in CFS is of multifactorial origin with some factors occurring as a consequence of the illness. The HPA axis may play a role in exacerbating or perpetuating symptoms later in the course of the disease.<sup>7</sup>
- 3.2.2 **Other neuroendocrinological factors:** studies have assessed the effects of growth hormone, dehydroepiandrosterone and its sulphate, melatonin, leptin, and neuroendocrine-monoamine interactions. There is some evidence from these studies to suggest alterations of dehydroepiandrosterone sulphate function and abnormal serotonin function in CFS, but it remains unclear as to whether these changes are of functional importance.<sup>8</sup>
- 3.2.3 **Immune dysfunction:** a variety of abnormalities have been reported including abnormalities in T cells and cytokine levels, although no consistent pattern of immunological abnormalities has been identified.<sup>9</sup>
- 3.2.4 **[Autonomic nervous system](#) dysfunction,** as demonstrated by [hypotension](#) and [postural orthostatic tachycardia syndrome \(POTS\)](#) occurring on head-up tilting on [tilt-table](#) testing, has been inconsistently implicated in the aetiology of CFS. Some researchers have reported characteristic changes that appear to differentiate CFS from most other conditions.<sup>10</sup> However, the precise nature of autonomic system involvement in CFS remains undetermined.<sup>11</sup>
- 3.2.5 **Infectious agents:** Many patients report that their illness commenced with an acute viral infection, with certain infections acting as a more common trigger than others. Glandular fever, viral hepatitis, and viral meningitis are followed by CFS in about 10% of cases, whereas common upper respiratory tract infections do not appear to trigger the disease.<sup>12</sup> A period of ill health arising prior to the apparent triggering infection may often be identified. The search for a viral causation has focused on [Epstein-Barr virus](#), human herpesvirus 6, group B coxsackie virus, human T-cell lymphotropic virus II, hepatitis C, enteroviruses, and retroviruses, among others. Non-viral infections, such as Q fever, have also been implicated. There has been no consistent evidence that CFS results from a single infectious agent. Rather, a [heterogeneous](#) group of

infections may trigger the symptoms of chronic fatigue syndrome. There is no evidence that chronic infection perpetuates the symptoms.<sup>11</sup>

3.2.6 **Immunisations:** A few case reports have suggested that CFS may occur after immunisations, but an association has yet to be confirmed by detailed studies. A placebo-controlled, double-blind study of the effect of influenza vaccine in CFS has shown no evidence of deterioration post-vaccination but a high level of symptoms evident both in those treated with the active vaccine and those who received the placebo.<sup>13</sup> Current advice given to health professionals to avoid immunisations during infections is designed to avoid any potential that may exist for triggering.<sup>12</sup>

3.2.7 **Psychiatric disorder:** The Fukuda criteria specify several major psychiatric illnesses as exclusion factors for CFS. However, many non-psychotic psychiatric disorders are not exclusionary for the diagnosis of CFS, and depression and anxiety states may be difficult to differentiate from CFS, as the symptoms are similar. Patients with CFS have an increased prevalence of current and lifetime mood disorders, primarily depression, compared to other chronically ill subjects or healthy comparison subjects. Generalised anxiety disorder and [somatoform disorders](#) also occur more frequently in patients with CFS than in the general population. In most, but not all cases, the mood or anxiety disorder precedes the onset of CFS. Despite this significant comorbidity with psychiatric conditions, there is evidence to suggest that CFS is not solely a manifestation of psychiatric disorder.<sup>11</sup>

3.2.8 **Familial:** a familial predisposition for CFS has been suggested.

3.2.9 **Sleep disorder:** Despite some reports of abnormal findings, the studies carried out in this field have failed to show a consistent or diagnostic sleep disturbance. However, some authorities view the condition as a non-restorative sleep disorder.

3.2.10 **Awareness of bodily sensations:** The exacerbation of fatigue by exertion appears to be mediated by a central mechanism rather than by some pathological process in the muscles themselves. Objective findings from exercise and pain testing in chronic fatigue syndrome patients have been suggestive of perceptual distortions in assessing bodily sensations. This mechanism is called central sensitisation.

3.3 CFS can be regarded as a condition in which physiological and psychological factors may combine to **predispose** an individual to the illness, and to **precipitate** and **perpetuate** the illness.<sup>11</sup> Regardless of the underlying aetiology, the manner in which patients with CFS perceive themselves, categorise their symptoms, appraise stressors, and adopt coping strategies will have a substantial effect on the course of the disease. Thus it is important for treating clinicians and their patients to avoid becoming embroiled in disputes over what has prompted the illness, and to focus instead on overcoming obstacles that stand in the way of recovery. This is the cognitive behavioural model of CFS.

3.3.1 **Predisposing factors** are considered to involve lifestyle, work stress, and personality. Controversy remains over the role of the premorbid personality in

the genesis of CFS. There is evidence both for and against the possibility that certain personality traits might predispose people to develop CFS.<sup>12</sup> Some patients appear never to have functioned well. Others report a “high-powered” lifestyle, often accompanied by an unwillingness to decline additional tasks, leading to over-commitment and overwork prior to the onset of the illness.<sup>14</sup>

- 3.3.2 **Precipitating (or triggering) factors** include viral infection, and acute physical stress such as trauma and surgery.<sup>14</sup> It has been reported that patients with CFS are more likely than population controls to have experienced severe events and difficulties in the 3 months prior to the onset of their illness.<sup>15</sup> However, evidence that life events can trigger CFS remains weak. It may be more likely that severe life events trigger mood disorders that in turn cause fatigue, rather than CFS itself. Nevertheless, clinical and patient experience suggests that increased “stress” may be common around the onset of symptoms or a triggering event, such as infection. It is unclear whether this is as a predisposing, triggering, or a maintaining factor. It is more generally accepted that, in some patients with CFS, emotional and physical stress can trigger exacerbations of the illness.<sup>12</sup>
- 3.3.3 **Perpetuating factors** present obstacles to recovery. They include inactivity and inconsistent activity, sleep disorder, depression, and a misunderstanding of the illness with a fear of making it worse (including catastrophic thinking about the consequences of increased physical activity and fixed illness beliefs). In some cases, these obstacles may be reinforced by the attitudes of relatives, health professionals, and/or patient support groups and mechanisms. Some of the literature that is available to patients may act as an obstacle to recovery. Perpetuating factors are considered in more detail in the following section on prognosis.

## 4. Prognosis

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- 4.1 Prognosis is extremely variable. Some patients recover relatively quickly, but in others the illness is more prolonged, and in a minority, the duration is very long. Although most patients improve over time, health and functioning rarely return completely to the individual's previous healthy levels, and a significant minority become severely and perhaps permanently disabled. In some patients, the condition follows a fluctuating course.<sup>12</sup> These conclusions are consistent with research that has shown that, while 17%-64% of patients with CFS improve, less than 10% achieve a full recovery, and 10%-20% worsen during follow-up. Most of these studies have involved referred patients, and outcomes in primary care may be better.<sup>11</sup>
- 4.2 The natural response of most patients to their sensation of fatigue is to reduce their activity for fear of exacerbating their symptoms (fear-avoidance behaviour). However, coping strategies of this nature are undesirable, as excessive rest and a focus on symptoms are associated with increased functional disability. Approaches to treatment that have found favour include: a consistent pattern of activity, rest and sleep (pacing); a gradual return towards normal activity (graded activity); ongoing review of any misinterpretation of symptoms and replacement with a physiological explanation of symptoms; and problem solving of current life difficulties. It may also be helpful for patients to adopt sleep management strategies (sleep hygiene) designed to promote regular sleeping patterns and to limit the time spent in bed.
- 4.3 The best medical evidence for effectiveness of treatment attaches to **graded physical exercise** and **cognitive behavioural therapy**. The most beneficial regime may be one that **combines** the **rehabilitative** approach of a graded increase in activity with a **psychological** approach to address any thoughts and beliefs about CFS that may be impairing recovery.<sup>5</sup>
- 4.4 **Pacing** entails a different approach that has considerable support amongst patients, voluntary organisations, and some clinicians. It provides an energy management strategy, which usually involves living within the limitations imposed by the illness and avoiding levels of activity that exacerbate symptoms. Once a baseline of sustainable activity is established, gradual stepwise increases are encouraged. The research findings on pacing are currently limited.<sup>12</sup>
- 4.5 Numerous other interventions have been suggested for CFS, with approaches ranging though pharmacological products, nutritional supplements, immunological substances and complementary/alternative therapies. No convincing evidence of efficacy exists for any of these treatments; intravenous **immunoglobulins** and oral hydrocortisone have demonstrated some limited effects but, overall, the evidence has been inconclusive.<sup>16</sup> Although the role of antidepressants remains uncertain, they may be advocated on a pragmatic basis, given their potential value in moderating problems related to pain, sleep, and energy, as well as mood.
- 4.6 A conviction held by the patient that their symptoms are attributable to a solely physical cause is the single most consistent predictor of a poor outcome.<sup>4</sup> Other factors that have been associated with worsening symptom severity over time include lower socioeconomic status, being unemployed, worse mental health, and more use of sedating and antidepressant medication.<sup>17</sup> Poor outcome has also been associated with membership of a self-help group, being in receipt of sickness benefit at the start of

treatment, and [dysphoria](#) as measured by the Hospital Anxiety and Depression scale.<sup>18</sup> Older age, longer illness duration and comorbid psychiatric disease have also been implicated.<sup>11</sup> Adherence to treatment is the best prognostic factor.

- 4.7 Many patients report that their illness was exacerbated by a premature return to work. Some will seek a change of career. As with other activities, the approach taken to a return to work either in the patient's previous job or in a new occupation needs to be planned, so as to be graduated but also time-targeted. The most favourable prognostic factors for return to work include disability duration of not more than 4 months, age onset of treatment of up to 30 years, not receiving disability payments, and an illness duration of not more than 40 months. Rehabilitation is rare after one year of work disability.<sup>14</sup>

## 5. Summary

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- 5.1 CFS is characterised by disabling physical and mental fatigue, disproportionate to the level of exertion, occurring in the absence any conventional physical or psychological disorder that would explain the problem.
- 5.2 The underlying cause of CFS remains unknown, and the syndrome appears to represent a [heterogeneous](#) disease whereby a number of mechanisms manifest with similar symptoms. For practical purposes, it is helpful to consider CFS as a condition that is subject to predisposing, precipitating and perpetuating factors.
- 5.3 Maladaptive coping strategies that involve excessive rest and a focus on symptoms are associated with increased functional disability. The most effective treatment currently available is considered to be [cognitive behavioural therapy](#), accompanied by graded physical exercise.

## **6. Related synopses**

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Fibromyalgia

## 7. Glossary

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| autonomic nervous system                         | Neurons that are not under conscious control, responsible for regulating key functions including activity of the heart muscle, smooth muscles (e.g. of the gut) and glands.  |
| cognitive behavioural therapy (CBT)              | A group of therapies that aim to reduce dysfunctional emotions and behaviour by altering thinking patterns and modifying behaviour.  |
| cortisol   | The major adrenal glucocorticoid hormone, the effects of which include stimulation of the conversion of protein to carbohydrates and involvement in the response to stress.  |
| dysphoria  | Excessive pain, anguish, agitation, disquiet, restlessness, malaise.   |
| Epstein-Barr virus                               | The virus responsible for infectious mononucleosis (glandular fever).  |
| heterogeneous                                    | Consisting of elements that are not of the same kind or nature.  |
| hypotension                                      | Abnormally low blood pressure. Hence: postural hypotension - the manifestation of low blood pressure when rising from a chair or bed.  |
| hypothalamic-pituitary-adrenal axis              | A major part of the neuroendocrine system that controls reactions to stress. It involves the interactions of the hypothalamus, the pituitary gland and the adrenal glands.   |
| immunoglobulins                                  | A class of proteins that function as antibodies in the immune response.  |
| narcolepsy                                       | A sleep disorder associated with excessive daytime sleepiness and involuntary daytime sleep episodes.  |
| postural orthostatic tachycardia syndrome (POTS) | A condition characterised by an excessive increase in heart rate upon assuming an upright posture.   |
| somatoform disorders                             | A group of disorders characterised by physical symptoms for which there are no demonstrable organic findings or known physiological mechanisms, with a strong presumption that the symptoms are linked to psychological factors. |
| tilt-table                                       | A table with a top that can be rotated on its transverse axis during experimental investigation e.g. testing of cardiac response.  |

## 8. References

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