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Somatoform Disorders

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CHAPTER

5

Chronic Fatigue and Neurasthenia: A Review

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INTRODUCTION

This chapter reviews current knowledge about chronic fatigue syndrome (CFS) and neurasthenia. The central feature of these syndromes is severe chronic disabling fatigue, typically exacerbated by exertion and unexplained by any other medical condition.

The diagnosis of neurasthenia has fallen out of fashion in most Western medical cultures, but remains an important one in many other cultures, most particularly in the Far East.

CFS, along with many other similar syndromes defined by somatic symptoms, such as fibromyalgia, is a condition whose home both in medicine (as a functional syndrome) and in psychiatry (as a somatoform disorder) remains somewhat precarious. These functional disorders [1] are, however, of central concern to psychosomatic medicine in its broadest meaning.

GENERAL ISSUES

A Discrete Disorder?

Although CFS is often regarded as a discrete condition, much as neurasthenia used to be, the severity of the symptoms of fatigue is continuously distributed in the general population [2] and the case definition can also be regarded as simply defining cut-off points on these continua.

Somatoform Disorders. Edited by Mario Maj, Hagop S. Akiskal, Juan E. Mezzich and Ahmed Okasha

Organic or Psychogenic?

Is CFS an "organic" or a "psychogenic" disorder? This is an issue that arouses intense passions nowadays [3]. This is nothing new, however, since very similar disputes, passions, and polemics surrounded neurasthenia at the end of the nineteenth century [4].

The extreme organic position argues that CFS will be eventually found to be as firmly based in disease pathology as any other medical condition. Attempts to establish a conventional pathology (e.g., chronic infection) have however not yet succeeded. An extreme psychogenic view would be that CFS is a "pseudo-disease", not in fact rooted in biology, but rather representing a social construction based on psychological amplification of a normal somatic sensation of fatigue. Neither of these extreme positions is sustained by the evidence or helpful for patients. In clinical practice, an extreme organic position encourages patients to engage in an often endless search for a doctor who will find the pathology and prescribe the right medication, whilst they adapt themselves to having a chronic disease. The extreme psychological view ignores the demonstrable physiological disturbances associated with the condition and, if perceived as dismissive and rejecting, can paradoxically encourage the patients in a defensive entrenchment of the belief that they really do have a disease [5]. An aetiologically neutral and integrated perspective that recognizes CFS as real and that acknowledges the likely contribution of biological, psychological, and social factors is almost certainly the best basis for effective clinical practice [6].

Medical or Psychiatric Diagnosis?

Parallel with the debate about aetiology is the argument about whether CFS is most appropriately regarded as "medical" or as "psychiatric". For the same symptoms, the medical diagnosis may be CFS and the psychiatric diagnosis may be an affective, anxiety or somatoform disorder. It can be argued that neither of these diagnoses alone is adequate. The proper use of the DSM-IV axes allows the patient to be given both a medical (Axis III) and a psychiatric (Axis I) diagnosis: the final diagnosis may, for example, be CFS/generalized anxiety disorder. However, we ideally need a classification that avoids two diagnoses being given for the same symptoms. This is a task for the authors of the forthcoming DSM-V [7].

THE SYNDROME

History

CFS is certainly not a new illness. The description of neurasthenia from over 100 years ago sounds remarkably similar [8]. The term CFS was coined in

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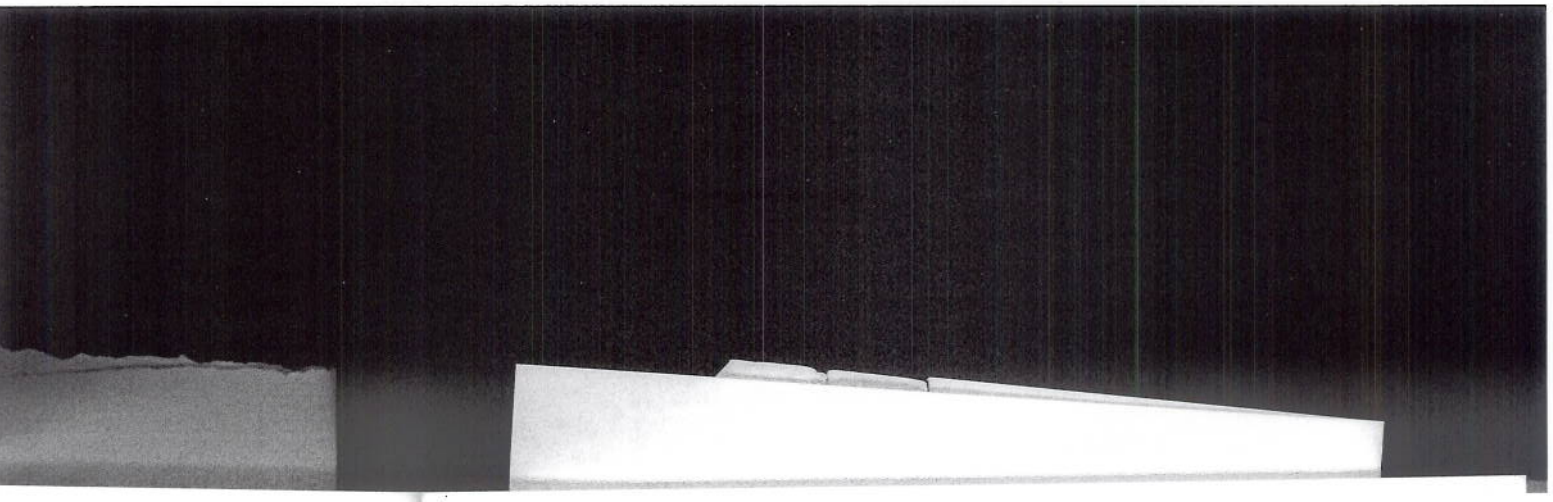

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1988 to describe a condition characterized by chronic disabling fatigue, with a large number of other somatic symptoms and strict psychiatric exclusions [9]. The authors of this early definition anticipated that a specific disease cause, possibly infectious, would be found, but this has never been established.

The term CFS subsumed a multitude of previous terms used to describe patients with similar symptoms. These include chronic Epstein–Barr virus infection, myalgic encephalomyelitis and post-viral fatigue syndrome, as well as neurasthenia (which remains a specific diagnosis in ICD-10). Patient advocacy groups have been very vocal and politically active in arguing that CFS is an inadequate description of their illness and that terms such as myalgic encephalomyelitis or encephalopathy or chronic fatigue and immune deficiency syndrome (CFIDS), which emphasize a medical pathology, are more appropriate. However, the concept of CFS does have the important advantage of being operationally defined and providing a basis for replicable scientific research.

Definition

A number of operational diagnostic criteria for CFS have been published. The first [9] that were in practice were found to be excessively cumbersome and restrictive. It was found that requiring multiple somatic symptoms as well as fatigue and using strict psychiatric exclusions made the condition very rare. Consequently, simpler and less exclusive case definitions were published [10, 11].

The most recent criteria, based on an international consensus, have been published in 1994 [12] (Table 5.1). Recommendations for their application have been recently further refined [13]. Whilst the different definitions have been a source of confusion and dispute, it should be remembered that all have been constructed by committees to aid research. Clinical practice should therefore not necessarily be tightly bound by them. The ICD-10 criteria for neurasthenia are summarized in Table 5.2.

Clinical Features

The clinical presentation of the individuals who meet the criteria for CFS is heterogeneous, although the core symptoms of fatigue exacerbated by exercise, subjective cognitive impairment, and disrupted and unrefreshing sleep are almost universally described, and some degree of widespread pain is common. Patients often report marked fluctuations in fatigue that occur from week to week and even from day to day. Most patients are not so disabled that they cannot attend an outpatient consultation, although some describe difficulty in walking or can only attend with the aid of wheelchairs

TABLE 5.1 Diagnostic criteria for chronic fatigue syndrome (adapted from Fukuda *et al.* [12])

Inclusion criteria

1. Clinically evaluated, medically unexplained fatigue of at least 6 months duration that is:
   - of new onset (not life long)
   - not a result of ongoing exertion
   - not substantially alleviated by rest
   - associated with a substantial reduction in previous level of activities
2. The occurrence of 4 or more of the following symptoms:

Subjective memory impairment, sore throat, tender lymph nodes, muscle pain, joint pain, headache, unrefreshing sleep, post-exertional malaise lasting more than 24 h.

Exclusion criteria

Active, unresolved or suspected medical disease; psychotic, melancholic or bipolar depression (but not uncomplicated major depression); psychotic disorders; dementia; anorexia or bulimia nervosa; alcohol or other substance misuse; severe obesity.

TABLE 5.2 ICD-10 diagnostic criteria for neurasthenia

(a) Either persistent and distressing feelings of exhaustion after minor mental effort, or persistent and distressing feelings of fatigue after minor physical effort.
(b) Accompanied by one or more of the following symptoms: muscular aches or pains, dizziness, tension headache, sleep disturbance, inability to relax, and irritability.
(c) Inability to recover through rest, relaxation, or enjoyment.
(d) Duration exceeds 3 months.
(e) Does not occur in the presence of organic mental disorders, affective disorders, or panic or generalized anxiety disorder.

and other appliances. Other patients remain bed bound and unable to visit a clinic: they represent an important and neglected group.

The symptom of fatigue is subjective, and there is a poor correlation between this feeling and objectively measured performance [14]. If patients with CFS are asked to perform exercise tests, they may not show the expected decrement, but rather report greater effort and increased fatigue, both at the time of the test and over the following days. Similarly, standard neuropsychological testing is usually normal, although often accompanied by complaint of greater effort [15]. There is some evidence that more complex cognitive tests do reveal deficits, although these usually appear less severe than those expected from the patient's subjective complaints and are hard to distinguish from those associated with depression [16].

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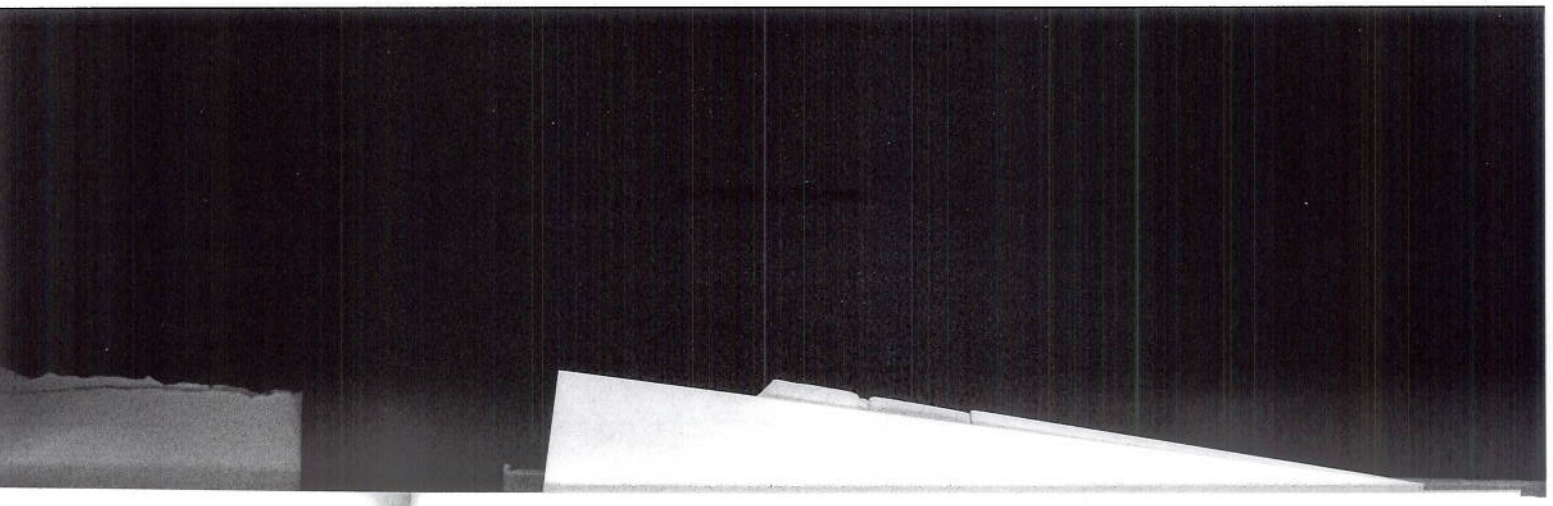

In summary, the core clinical features of CFS are physical and mental fatigue exacerbated by physical and mental effort. These are subjective phenomena, often less evident on objective testing. While some may interpret this observation as evidence of exaggeration of disability, it can also be interpreted as indicating the essentially subjective and sensory nature of this condition.

Primary or Secondary

CFS is diagnosed when the patient has no evidence of another medical condition. This makes it easy to define the symptoms as "medically unexplained". However, similar symptoms are often found in patients with other medical diagnoses. For example, symptoms of CFS have been identified in disease-free cancer patients [17] and in patients with multiple sclerosis [18]. The terms "primary" (occurring in the absence of another condition) and "secondary" (accompanying a medical condition) have been used to describe these findings. The terminology is however confusing and arguably more a matter of differential diagnosis than of comorbidity (see below). It is best avoided.

Association with Other Functional Somatic Syndromes

Studies that have assessed the comorbidity of CFS with other functional somatic syndromes have found high rates of migraine, irritable bowel syndrome, pelvic pain, and temporo-mandibular joint pain. These syndromes, like CFS, are associated with high lifetime rates of comorbid mood and anxiety disorders [19]. There are other similarities between CFS and these disorders, including a female predominance, association with childhood abuse, and treatment response patterns. This observation raises the possibility that all these functional syndromes have more in common than previously thought by the specialists who diagnose each [1, 20]. It has been further suggested that these syndromes, along with mood and anxiety disorders, share a common psychological and/or central nervous system pathophysiology [21].

Association with Psychiatric Disorders

In clinical practice, many but not all patients with CFS can be given a psychiatric diagnosis. Most will meet the criteria for a depressive or an anxiety disorder. The others are likely to meet DSM-IV criteria for a somatoform disorder or merit an ICD-10 diagnosis of neurasthenia [22]. The more somatic symptoms the patient has, the more likely is a diagnosis of depression or anxiety [23]. Precise prevalence rates of psychiatric disorders do however depend on the nature of the patient population studied and the diagnostic

criteria used. Several factors may influence the estimates obtained. First, compared to a community sample, patients attending clinics are likely to be more disabled and distressed and therefore to have more depression and anxiety. Second, some symptoms (such as fatigue, sleep disturbance, and poor concentration) overlap with those of depression and anxiety, and the observed prevalence of psychiatric disorders will depend on whether all symptoms are counted towards a diagnosis of psychiatric disorder, or those regarded as related to CFS are excluded. Third, it has been argued that atypical presentations of depression [24] and anxiety [25] are common in these groups, adding further unreliability to estimates of prevalence.

Fatigue is strongly associated with depression. The international World Health Organization (WHO) study of more then 5,000 primary care patients in a number of countries [26] found that 67% of cases of CFS (defined from survey data) also had an ICD-10 depressive syndrome [27]. Studies of clinic attenders with CFS have reported that more than 25% have a current DSM major depression diagnosis, and 50–75% a lifetime diagnosis [28]. Some features of CFS, such as chronic pain, are also strongly associated with depression in the general population [29].

One study reported generalized anxiety disorder in as many as half of clinic patients with CFS when the hierarchical rules that subsume it under major depression were suspended [30]. Panic disorder is especially common in patients with medically unexplained symptoms: a prevalence of 13% was reported in one study of CFS [31]. Panic should be suspected when symptoms are markedly episodic.

Post-traumatic stress disorder has been reported to have higher than general population prevalence in patients with CFS [32] and is associated with a report of previous abuse (see below).

Some CFS patients will meet criteria for hypochondriasis, because of persistent anxious concern about the nature of their illness. Others may meet the criteria for somatization disorder, because of a long history of multiple symptoms. The majority of patients with CFS who do not meet the criteria for anxiety or depression will fit the undemanding criteria for a diagnosis of undifferentiated somatoform disorder, but this is largely replacing one set of ignorance with another and does not advance the cause very far.

The association of CFS with psychiatric disorders appears not to be explained simply by overlapping symptoms, as it remains high even when fatigue is excluded from the diagnostic criteria for major depression [33, 34].

The occurrence of depression or anxiety disorders in patients with CFS cannot be attributed entirely to referral bias, as the rate is still elevated, although less so, in community cases. Neither does it appear that depression can be explained entirely as a reaction to disability, as it has been found to be more common than in patients with other chronic disabling medical conditions, such as rheumatoid arthritis [35]. In these studies, the absolute rates of

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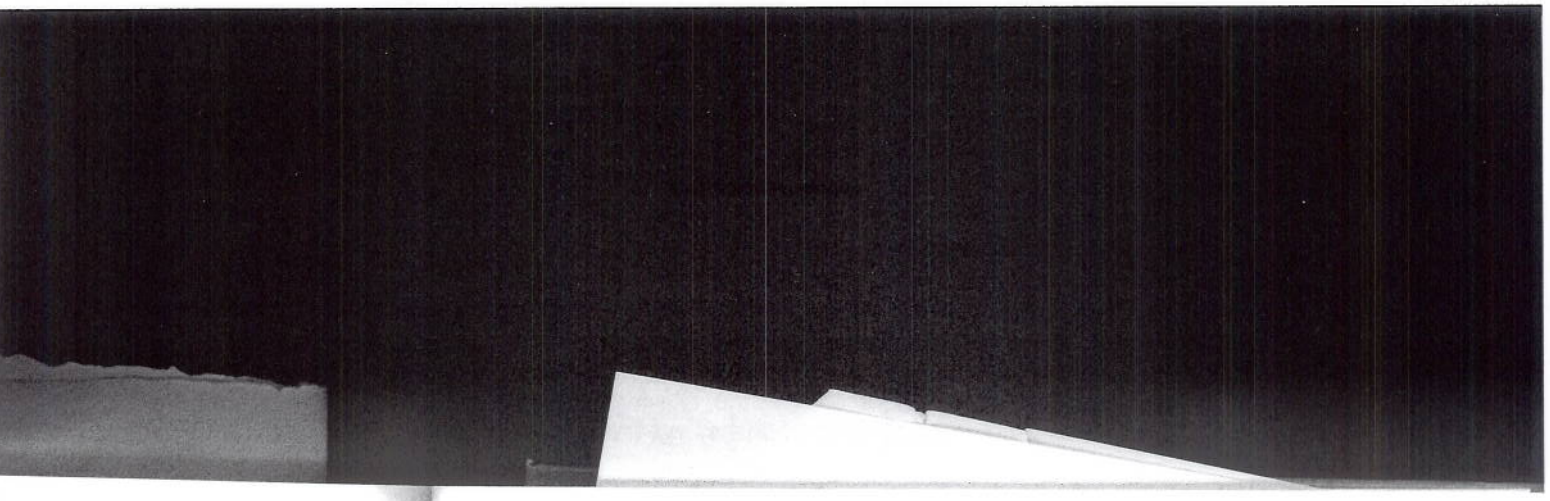

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psychiatric disorder vary, according to the vagaries of interviews, methods, and criteria, but what does not vary is the finding that rates are about two times higher in CFS patients than in those with other disabling medical conditions. However, many patients with CFS do not have depressive and anxiety syndromes, even after detailed assessment [34].

The relationship with somatoform disorders is controversial, both theoretically and in the "real world". All disorders whose diagnostic criteria include a long symptom checklist but lack definitive "external" diagnostic features (biochemical, pathological or radiological) are certain to overlap. Ninety-five percent of those seen in a UK CFS clinic also fulfilled the criteria for neurasthenia [36], even if none of the patients had ever heard of the term, while 70% of those attending an Austrian clinic with the diagnosis of neurasthenia also fulfilled the criteria for ICD-10 undifferentiated somatoform disorder [37]. Whether this will get us very far is not clear: there is a danger of using one unexplained syndrome (e.g., CFS) to explain another (ICD-10 somatoform disorder), or vice versa.

It has been proposed that depression, anxiety and CFS have shared risk factors. These may include both genetic factors [38] and adverse experiences such as abuse and victimization [39]. The lack of acceptance by others of the suffering associated with these medically ambiguous conditions may also contribute to emotional distress [40].

EPIDEMIOLOGY

Fatigue is common, but CFS as currently defined is relatively rare. A large survey of 90,000 residents in Wichita, Kansas, which used rigorous assessment and exclusion criteria, found that whilst 6% of the population had fatigue of more than 1 month duration, only 235 per 100,000 (or 0.2%) had CFS [41]. It should, however, be noted that the application of current diagnostic criteria [12] excluded large numbers of patients, mainly because of diagnoses of rheumatoid arthritis and psychiatric disorder.

Few modern epidemiological studies have looked specifically at neurasthenia. In an Australian national sample that did include neurasthenia, prolonged and excessive fatigue had a population prevalence of 13%, but with substantial comorbidity. "Pure" neurasthenia was reported in 0.5% [42]. It was slightly commoner in the Zurich studies of Jules Angst, but again comorbidity with depression and anxiety was conspicuous [43].

CFS is more common in women: the sex ratio has been reported to be about four to one [41].

The most common age of onset for CFS is between 30 and 50 years. The syndrome is also diagnosed, although controversially, in children. A recent epidemiological study from the United Kingdom found a prevalence of CFS

of only 0.002% in 5–15-year olds [44]; another in the United States found it to be equally uncommon [45].

In the original nineteenth century formulation, neurasthenia was described as an illness associated with higher socio-economic status, of high achievers and "captains of industry". Likewise, when myalgic encephalomyelitis first became popular in the 1980s, it was labelled by the media as "yuppie flu". With the passage of time, neurasthenia descended the social scale, until it became one of the commonest diagnoses in very disadvantaged groups, such as New York garment workers. For CFS and its cousin fibromyalgia, new epidemiological studies have confirmed a higher prevalence in persons of lower socio-economic status and in those who have received less education [46, 47].

CFS is associated with substantial self-reported loss of function and substantial work disability [48]. Unemployment in patients with CFS attending specialist services in the United States was as high as 50% [49].

It is often noted that the diagnosis of CFS is almost entirely restricted to Western nations, whereas the symptoms of fatigue and pain are universal. It is unclear to what extent this reflects differing epidemiology or simply different diagnostic practice. The WHO Collaborative Study of Psychological Problems in General Health Care, conducted in 14 countries, reported wide variations in the prevalence of persistent pain (including both medically explained and medically unexplained) and fatigue [50, 51].

If we move from symptoms and research criteria to actual labels, the cultural variation is enormous. CFS, for example, is clearly a very big issue in the English-speaking world, Scandinavia, and Holland, but mysteriously is not talked about in most other countries. One can find the occasional paper from Italy, Spain, and Germany, but these usually reflect the interests of one or two clinicians. CFS seems to be ignored in the Francophone world, as indeed is neurasthenia. The same clinical territory is instead claimed by "spasmophilia", a concept virtually unknown to the rest of the world [52]. The obvious question is whether disorders such as CFS can be found in the Francophone world, but are ignored (as some argue). One paediatrician returning to practice in France after a period of working in England was astonished by the absence of any cases of severe CFS in French children, whereas they had formed a demanding part of his practice in London [53]. He argued that it would be inconceivable that children with the level of disability that he had witnessed in England (confined to bed or wheelchairs and unable to undertake any form of education) could have been overlooked in France, if they existed.

Our hypothesis is that fatigue syndromes are universal, but that culture is important in understanding the transition from symptoms to disability. Where there is considerable concern around concepts such as immune dysfunction, viral persistence, and environmental toxicity (irrespective of

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PROGNOSIS

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ETIOLOGY

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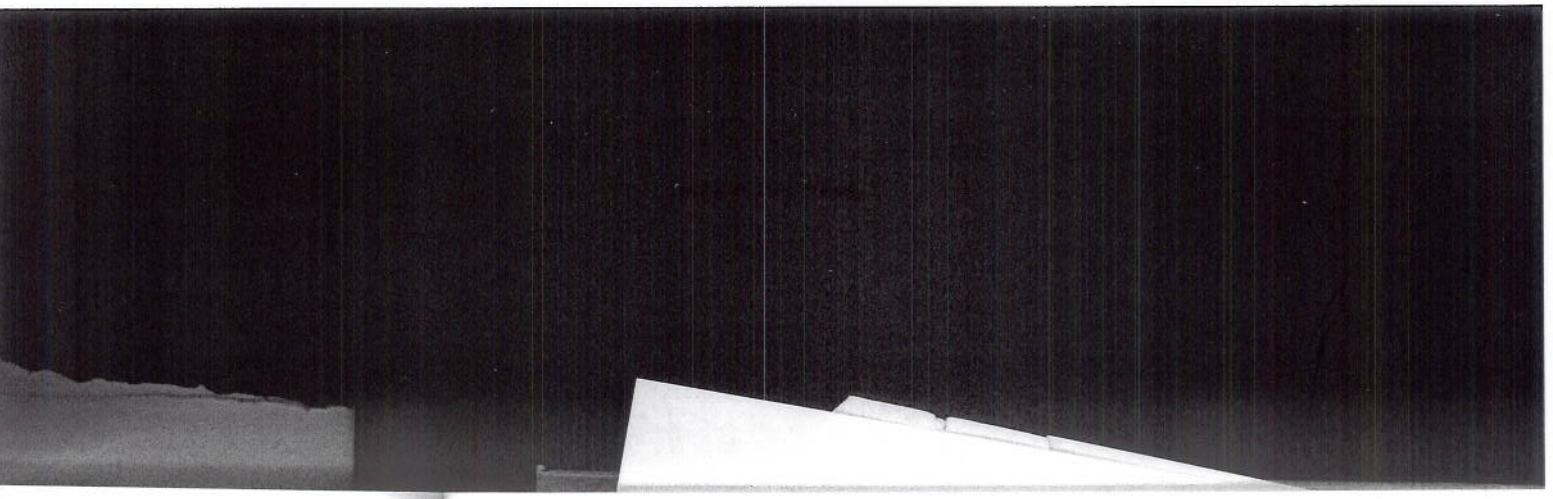

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Finally, the vicissitudes of the diagnosis of neurasthenia in China are such that this topic deserves a separate text of its own. Arthur Kleinman will be forever associated with his studies of neurasthenia in Chinese society, suggesting that it was a culturally sanctioned expression of distress, akin to depression, where more "psychological" forms of distress would be less acceptable and seen perhaps as a political gesture [54]. Sing Lee has argued that even this complex formulation does not do justice to Chinese concepts of health and illness, and in particular mind and body [55].

PROGNOSIS

The prognosis for patients with CFS is variable. The condition typically has a chronic but fluctuating course. Prospective studies in the general population report that about half of CFS patients have partial or complete remission at 2–3 years [56].

Poor outcome in CFS is predicted by longer illness duration, more severe symptoms, older age, depression, and lack of social support [57], and also by a strong belief in physical causes [58]. Severely disabled patients attending specialist clinics have a particularly poor prognosis [59].

ETIOLOGY

The precise aetiology of CFS remains unknown. A wide range of factors have been proposed, but none unequivocally established. The available evidence may be summarized as suggesting that a combination of environmental factors and individual vulnerability initiates a series of social, psychological, and biological processes that lead to the development of CFS (Table 5.3).

These factors will be discussed under the headings of predisposing, precipitating and perpetuating factors. It is worth noting that, with notable exceptions, most research in this area is based on small case–control studies (typically 10–20 patients per case and control group) with insufficient power to control for confounding variables, thereby limiting our ability to draw strong causal inferences about any of the findings reported below.

Predisposing Factors

Biological Factors

There is modest evidence from family and twin studies for genetic factors playing a part in predisposing individuals to CFS. A small study found that

TABLE 5.3 Possible aetiological factors to consider in a formulation of chronic fatigue syndrome

	Predisposing	Precipitating	Perpetuating
Biological	Genetics	Acute disease or injury	Neuroendocrine changes Deconditioning Sleep disorder
Psychological	Personality	Perceived stress	Depression Fixed disease attribution Catastrophizing Low self-efficacy Avoidance of activity
Social	Lack of support	Life events	Information Lack of legitimacy of illness Social or work stress Occupational and financial factors

individuals with a family member with CFS are more likely to also have the condition [60]. In a study of 146 female–female twins, one of whom had CFS, the concordance was 55% in monozygotic and 20% in dizygotic twins [61], suggesting moderate heritability and also the importance of environmental factors.

Psychological and Social Factors

A predisposing personality type is often commented on by clinicians, but has been little studied. The clinical observation that CFS patients lead abnormally active lives prior to becoming ill has received limited empirical support [62].

Childhood and adult neglect, abuse, and maltreatment have been reported by some, but not all studies, to be more common in CFS than in medical comparison groups [39].

Low social status and lower levels of education seem to be risk factors (see above).

Precipitating Factors

Biological Factors

There is good evidence that infection can precipitate CFS, whilst the historical literature on neurasthenia frequently reported post-infective onset, the main culprits being influenza and typhoid fever.

Modern epidemiological research has failed to confirm the association with influenza [63], and typhoid fever has yet to be studied. Instead, prospective studies have found that the specific infections associated with the

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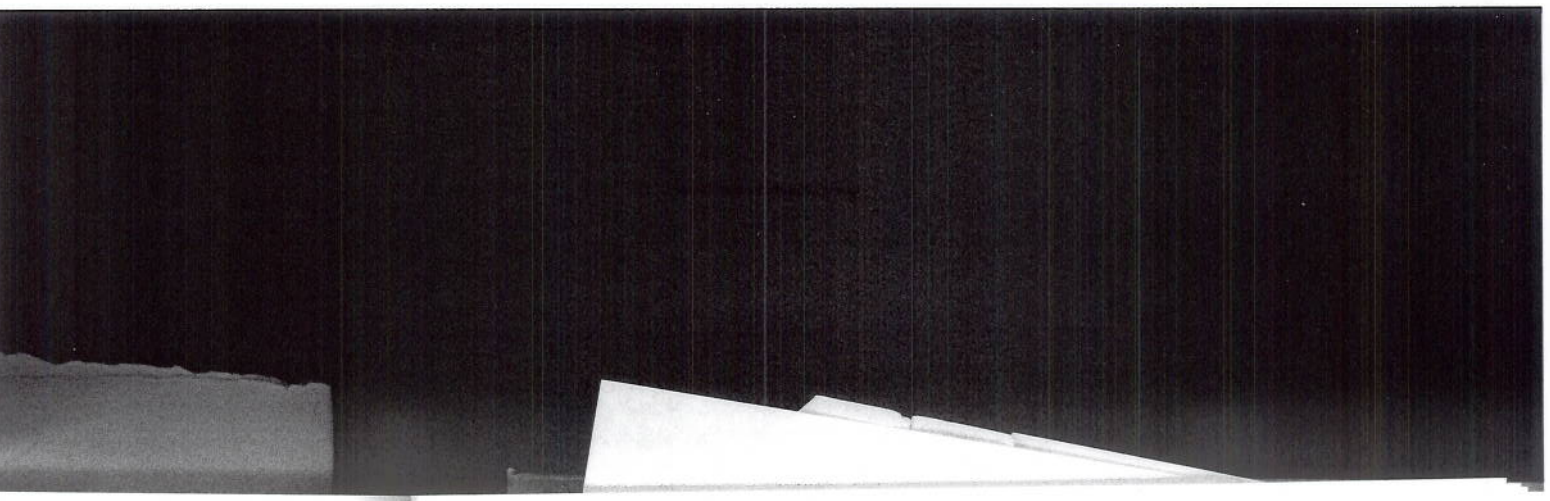

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subsequent development of CFS include Epstein–Barr virus infection [64], Q fever [65], viral meningitis [66], and viral hepatitis [67]. The aetiological mechanisms to explain these associations remain unclear, but may include both immunological factors and an acute reduction in activity [64] (see perpetuating factors below).

The role of physical injury in the aetiology of CFS has been controversial, in part because of the implications for legal liability and compensation. In general, traumatic explanations of CFS are not very common, as compared, for example, to infective triggers [68].

Psychological and Social Factors

Clinical experience indicated that patients often report the onset of CFS as occurring during or after a stressful period in their lives. The evidence for life stress or life events being a precipitant of CFS is however both limited and retrospective [69]. One of the best studies so far examined 64 cases and a similar number of matched controls. An excess of severe life events and difficulties was found in the CFS cases for the year prior to onset. More specifically, a certain type of life events called *dilemmas* (defined as events when the person had to choose between two equally undesirable responses to circumstances) was found in one-third of CFS cases and none of the controls [70].

Perpetuating Factors

Biological Factors

There has been much interest in the potential role of ongoing infection and associated immunological factors, not least because many of the symptoms of CFS remind sufferers of those of viral infections. It was previously thought that chronic Epstein–Barr virus infection was a cause of CFS, but that hypothesis has been rejected, to be replaced by much sounder evidence that this infection has a particular propensity to trigger CFS [64]. There have been numerous reports of chronic infection with other agents in CFS, but no compelling evidence has been presented.

Immunological factors, especially cytokines, have also been much investigated in CFS, not only because of the possible triggering effect of infection, but also because administration of immune active agents, such as interferons, is recognized as a cause of fatigue and myalgia [71], and because similar symptoms in conditions like hepatitis C have been associated to changes in measured cytokines [72].

A variety of immune changes have been reported in patients with CFS. Chief amongst these are lowered natural killer cell activity and a modest

immune activation, but the results have been difficult to replicate and bring together [73]. Once again, the direction of causality is unclear—are these, for example, secondary to the modest hypocortisolaemia that is frequently reported? The hypothesis that CFS is associated with immune activation therefore remains tantalizing, but unproven.

The bulk of evidence indicates that there are no proven pathologic or biochemical abnormalities of muscle or muscle metabolism, either at rest or with exercise, other than those associated with deconditioning. Deconditioning describes the physiological changes that lead to the loss of tolerance of activity after prolonged rest (as a result of pain, for example). It has been found in many but not all patients with CFS [74, 75]. Deconditioning offers a potential biological explanation for exercise-induced fatigue and worsening or persistent muscle pain in patients with CFS, and also provides a rationale for treatment using graded activity (see below).

Patients with CFS typically complain of unrefreshing and broken sleep, a symptom that has been objectively confirmed using polysomnography. Abnormalities in sleep have been claimed to be of major aetiological importance, but their significance remains unclear [76].

A core finding in CFS is that patients report greater cognitive effort and more cognitive impairment than is detectable on objective assessment. Or, to put it another way, CFS is a disorder of effort perception, both physical and mental. Patients require additional central resources to produce the same amount of mental work, as neuroimaging is starting to demonstrate [77], and consistently underestimate their performance relative to normal performance [78]. This has been repeatedly shown not just in neuropsychological studies, but also in studies of exercise tolerance (see [79]). Abnormal perception of sleep has also been found in CFS [80]. The source of these abnormal perceptions is unclear, and will require a careful investigation. Is it a primary central information processing abnormality? Alternatively, is it the consequence of avoidance of demanding tasks? Irrespective of the cause, one consequence should be a shift away from unrewarding attempts to show static structural lesions in the central nervous system to studies of what is actually impaired in CFS—the dynamics of physical and mental effort.

One of the best-supported biological abnormalities reported to be associated with CFS is a change in neuroendocrine stress hormones. A repeated observation has been a tendency to low blood cortisol and a poor cortisol response to stress [81]. This finding differs from what would be expected in depression (in which blood cortisol is typically elevated) but is similar to that reported in other stress-induced and anxiety states. It is unclear whether this is a primary abnormality or merely a consequence of inactivity or sleep disruption, but recent evidence is starting to suggest that the changes are multifactorial, and might be a consequence of illness. They seem to be reversed by behavioural interventions (see [82]).

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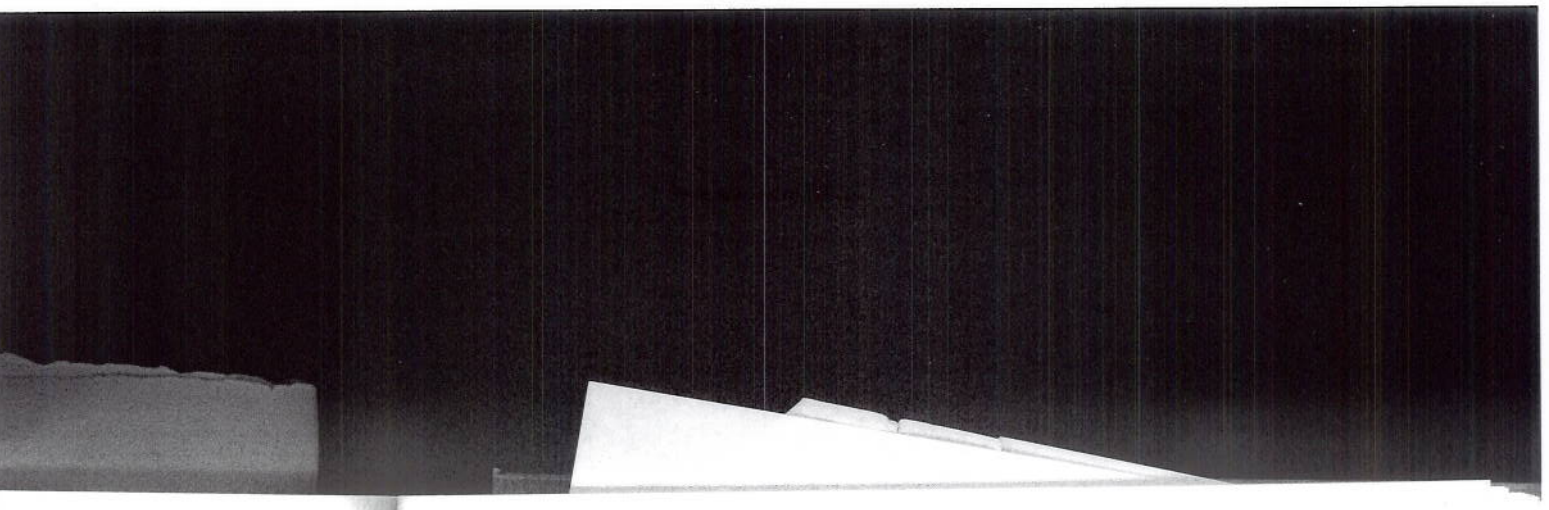

Failure to maintain blood pressure when assuming erect posture (orthostatic intolerance) and particularly a pattern in which the heart rate increases abnormally (postural orthostatic tachycardia syndrome) have been reported in CFS [83]. This finding has been interpreted as indicating abnormal autonomic nervous system function. However, postural hypotension occurs after prolonged inactivity [84], and its specificity to CFS remains unclear.

The brains of patients with CFS are probably structurally normal, although minor abnormalities have been reported in a minority of patients [85]. A small magnetic resonance imaging study suggested a deficiency of brain choline in patients with CFS compared with healthy controls [86].

The use of functional brain imaging has great potential to elucidate the biology of syndromes such as CFS in which the source of fatigue is felt to be central rather than peripheral. An early single photon emission computed tomography (SPECT) study [87] and a positron emission tomography (PET) study [88] reported reduced brain stem perfusion in patients with CFS. However, another study found fewer differences when CFS was compared with depressed patients, reminding us of the need for careful control for variables such as depression [89]. There is evidence of more widespread cerebral activation in CFS patients than controls when performing a fatiguing cognitive task [90]. Although tantalizing, these functional brain imaging findings must be regarded as preliminary. Furthermore, evidence of changes in brain activation or brain reorganization should not be taken to mean that the symptoms are necessarily based in fixed neurological pathology; behavioural rehabilitation and drug therapy can potentially reverse such changes [91].

Psychological and Social Factors

Although the cause of CFS is unknown, many patients, and especially those seen in specialist clinics, strongly attribute their symptoms to a physical disease [92]. A systematic review of prognostic studies in CFS found that such strong attributions predicted a poorer outcome [58]. The mechanism of this effect is unclear. It may be because such an attribution favours focusing attention on symptoms, more passive coping, and greater inactivity [93], or alternatively, it may lead to non-participation in potentially effective psychological and behavioural treatment (see below).

Catastrophizing is a tendency to make excessively negative predictions about symptoms, for example, "If I do more, my pain or fatigue will keep getting worse and worse". Catastrophizing has been observed in patients with CFS [94] and is associated with increased symptom vigilance and avoidance of activity, and more severe disability. Furthermore, a reduction in the belief that activity is damaging is associated with recovery during rehabilitative therapy [95], suggesting that it may be a critical psychological target for effective rehabilitation.

Self-efficacy is the belief that one can do something, despite symptoms. It has been found to be low and this has been associated with more severe disability in patients with CFS [96]. Achieving an increase in self-efficacy is another potential target for treatment that aims to improve function.

Patients cope with their symptoms in different ways. The way a patient copes will also be influenced by his illness beliefs [97]. Of particular interest is coping by avoiding any activity that it is feared will exacerbate symptoms. This "fear-avoidance" phenomenon is well established in chronic pain patients [98] and has also been observed in CFS [99] and in fibromyalgia [100]. Objective assessment also confirms that patients with CFS show reduced overall activity, with most patients oscillating between activity and rest, and a quarter being more pervasively inactive. This reduced activity produces deconditioning, and increasing activity is a treatment task.

Another potentially important coping behaviour is the focusing of attention on symptoms, so-called symptom focusing or symptom vigilance [101]. This behaviour is, not surprisingly, associated with catastrophizing beliefs and greater perceived symptom intensity. It offers another target for treatment.

Patients' beliefs about their illness and associated coping behaviour will be influenced by the information received from others. A striking social aspect of CFS is the high level of activity of patient support and advocacy organizations, mainly over the Internet [102]. Studies from the United Kingdom have reported that patients who are members of a support group have a poorer outcome, despite similar illness duration and disability [103], and a poorer response to rehabilitation [104]. It is unknown whether this reflects self-selection into such groups or the effect of the group on patients' beliefs, coping, and willingness to engage in rehabilitation. Other factors include the experience of repeated questioning of the legitimacy of one's illness by doctors and others, which probably serves to drive some patients to join advocacy organizations [3,105]. Perhaps unsurprisingly, in fibromyalgia, the acquisition of a disability pension is also associated with a worse prognosis [106].

Summary

In summary, there is some suggestive evidence that patients are predisposed to develop CFS by some combination of genetic factors, previous experience, and possibly lack of social support. Many patients with CFS give a history of preceding infection. Others can identify no precipitant. Most research has been into factors associated with established illness, so-called perpetuating factors, as these are both clearly more accessible to study and more relevant to treatment of established cases.

A large number of biological factors have been investigated, with interest initially being directed at peripheral nerves and muscles and subsequently focusing on the central nervous system and its neuroendocrine and autonomic

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DIAGNOSTIC EVALUATI

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The physiological effects of inactivity seem to be important. There is substantial evidence for the importance of psychological and behavioural factors, especially the fear of exacerbating symptoms and the associated avoidance of activity. Social factors are harder to study, but often of striking importance clinically.

Models of CFS

The above findings can be amalgamated into models. There are three main models corresponding to biological, psychological, and social perspectives, although in reality all three are probably relevant.

It is well known that the immune and central nervous system interact and also have reciprocal relationships with sleep and activity. It is therefore possible to construct a tentative biological model in which these interact to perpetuate the illness [107]. There seems to be evidence for the role of infection triggering CFS and perhaps some neuroendocrine mechanisms acting to perpetuate illness.

Whatever the biological aspects of CFS, cognitive-behavioural models assume that the symptoms and disability are perpetuated, at least in part, by psychological, behavioural, and social factors. Biological factors are assumed to be either only partially responsible for the illness or largely reversible [108]. The cognitive-behavioural models for chronic pain and CFS have much in common [98]. Both emphasize the importance of fear of symptoms leading to focusing on the symptoms, helplessness, and avoidance of activity. This model provides the rationale for behavioural and cognitive-behavioural approaches to rehabilitation (see below).

The third model emphasizes the role of social factors in shaping the illness. A fight for the legitimacy of the syndrome as a chronic medical condition is central [109]. Patient advocacy has been strongly hostile to psychological and psychiatric involvement, probably because it is seen as undermining legitimacy. The social model proposes that patient organizations, whilst providing valuable social support, can also shape patients' illness beliefs, medical care, and disability payment seeking in ways that are not conducive to recovery [110].

DIAGNOSTIC EVALUATION

Effective management of patients with possible CFS and/or neurasthenia requires first that alternative medical and psychiatric diagnoses are considered and second that the patient receives a comprehensive assessment upon which to collaboratively plan management.

Identifying Medical and Psychiatric Conditions

Medical Differential Diagnosis

The medical differential diagnosis for CFS and linked conditions is a long one, as many diseases present with pain and/or fatigue [111]. A physical examination must therefore be performed in every case to determine any alternative medical diagnoses. As with many chronic diseases, particularly rheumatologic conditions, time is often the principal arbiter as the conditions evolve clinically. For symptoms in general, 75% of patients presenting to primary care improve within 2–4 weeks [112]. Thus, it makes sense to rely on an initial 4–6 week wait to clarify whether the symptoms will be persistent [113]. For persistent symptoms, most of the common medical diseases can be diagnosed from a standard history, physical examination, and basic laboratory studies.

When symptoms exceed 4–6 weeks, basic investigations are appropriate. The following have been found to be adequate as screening tests: thyroid-stimulating hormone, erythrocyte sedimentation rate (sensitive for any condition with systemic inflammation), complete blood count, and basic chemistries. Withdrawal of some medications (particularly statins) is also appropriate.

Special investigations should only be carried out if clearly indicated by history or examination. Immunological and virological tests are generally unhelpful as routine investigations and remain research tools. Sleep studies can be useful in excluding other diagnoses, especially when the fatigue is characterized by sleepiness: these include sleep apnoea, narcolepsy, nocturnal myoclonus, and periodic leg movements during sleep. Once symptoms become chronic (>3 months) and remain unexplained, the general approach is to avoid excessive testing, establish regular follow-up, screen for depressive and anxiety disorders, and focus on symptoms management.

Those concerned about missing a serious medical diagnosis can be reassured that in most cases the primary care physician's initial judgement in this regard is likely to be accurate [114]. However, there is some evidence that CFS may be over-diagnosed by primary care physicians [115], and psychiatrists should feel able to request second medical opinions.

Psychiatric Differential Diagnosis

The under-diagnosis of psychiatric disorders is particularly common [116], probably reflecting a focus of the initial medical assessment on somatic symptoms and a tendency to disregard mood changes as simply being a consequence of these. The most important psychiatric diagnoses to consider are depressive and anxiety disorders, because of their frequency and their

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Assessment of the Illness

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MANAGEMENT

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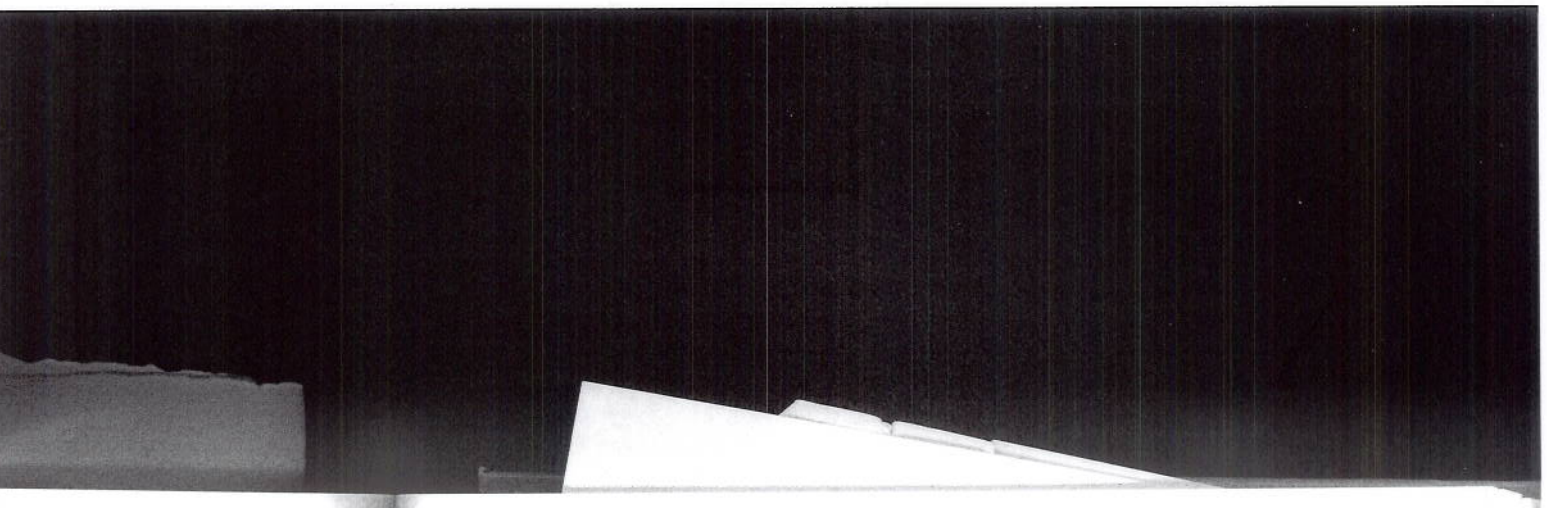

implications for treatment. Depression may be "masked" and require expert assessment. Panic attacks with agoraphobia may cause intermittent severe fatigue and disability. Somatoform disorders are common, but have fewer implications for management. A diagnosis of somatization disorder indicates a poorer prognosis and hypochondriasis indicates special attention to repeated reassurance seeking, which may perpetuate fears of undiagnosed disease [117].

Assessment of the Illness

Other than making diagnoses, the aims of the assessment are: (a) to establish a collaborative relationship with the patient, (b) to elicit the patient's own understanding of his illness and how he copes with it, and (c) to identify current family and social factors such as employment and litigation that may complicate management. It is important to inquire fully about the patient's understanding of his illness (e.g., "what do you think is wrong with you?" or "what do you think the cause is?"). Patients may be fearful that their symptoms indicate a severe, as yet undiagnosed, disease or that exertion will cause a long-term worsening of their condition. A formulation (see Table 5.3) that identifies potential predisposing, precipitating and perpetuating factors is valuable both in providing an individualized explanation to the patient and for targeting interventions.

MANAGEMENT

Agreeing on a Diagnosis, Formulation and Management Plan

Forming a Therapeutic Relationship with the Patient

The patient will have often seen many other doctors and will have experienced problematic interactions with them [105]. Other doctors may have offered overly biomedical or overly psychological explanations, or even dismissed the patient completely.

How to Explain Psychiatric Involvement

Psychiatrists' involvement in management may be interpreted by the patient as indicating that their condition is considered to be "all in their head". It is often best to begin with a somatic assessment and only then to introduce discussion of psychological factors. This is best done in a non-blaming and normalizing way. For example: "You have clearly had a terrible time made

worse by not being believed. It is entirely understandable that this has got you down". It is generally unhelpful to force a psychiatric diagnosis on an unwilling patient. It is also important to explain how treatments commonly associated with psychiatry (particularly antidepressant medication and cognitive-behavioural therapy, CBT) do not necessarily imply that the person is mentally ill. Rather, they can be explained as ways of normalizing brain and bodily function in conditions that are exacerbated by stress.

Giving the Diagnosis

It is important to give the patient a positive diagnosis supplemented with an aetiological formulation. There is some controversy about whether giving patients a diagnosis of CFS is helpful or harmful [118]. There are those who feel that a diagnosis enables patients to both conceptualize their illness and communicate about it with others [119]. Others are concerned about the potentially harmful effect of a diagnosis, arguing that it medicalizes and pathologizes symptoms in a way that can exacerbate social and occupational disability [120]. The particular label of myalgic encephalomyelitis, used in the United Kingdom as a popular term for CFS, carries with it the connotation of an organic inflammatory disease of the central nervous system, as well as numerous other cultural "tropes".

In a large study using the General Practice Research DataBase, it was found that patients with the label of myalgic encephalomyelitis seemed to do worse than those with the label of fibromyalgia or post-infective fatigue syndromes [121]. In our clinical experience, what matters less is the label, and more what information is given after the act of diagnosis. A positive diagnosis linked to an explanation of the potential reversibility of symptoms and a management plan to achieve this is an essential starting point for effective management.

Offering an Explanation

This should ideally be scientifically accurate, acceptable to the patient, and congruent with the management plan. It can be explained that, whilst the specific causes of CFS or fibromyalgia remain unknown, a combination of vulnerability and environmental stress involving the brain and the endocrine system are most likely. One such explanation is that the illness is a disorder of brain function rather than *structure*; that is, a "functional" nervous disorder [122].

The Management Plan

This should be explained to the patients as following from the formulation, focusing on illness perpetuating factors and consisting of elements aiming to

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General Measures

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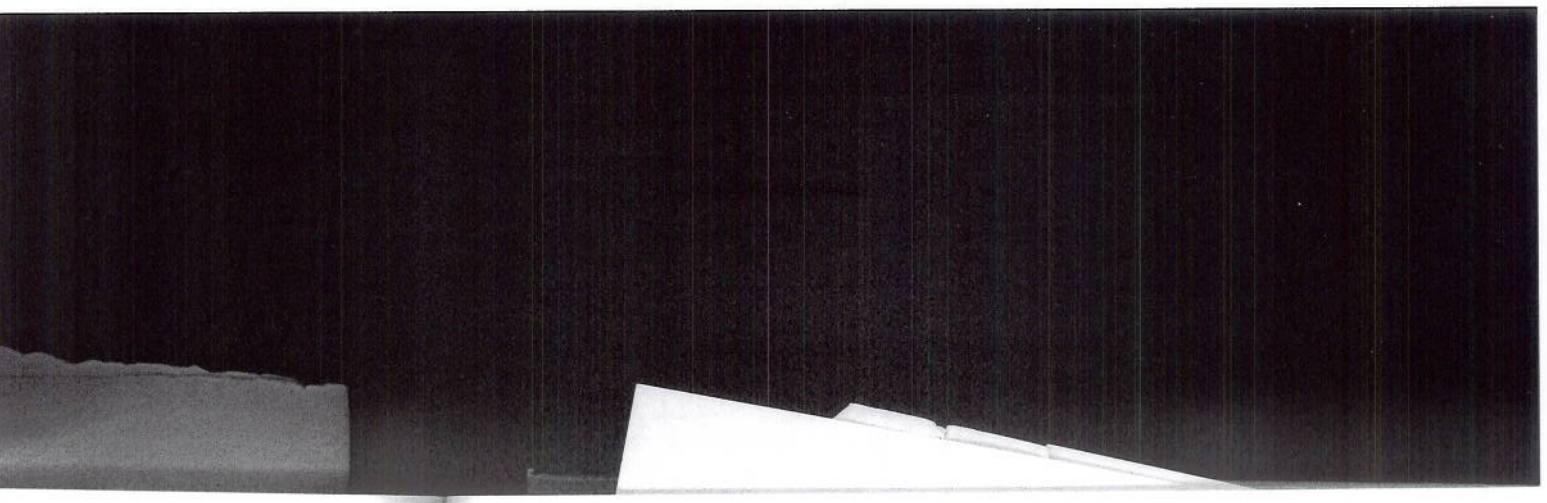

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(a) relieve symptoms such as depression, pain, and sleep disturbance with agents such as antidepressants, (b) assist the patients efforts at coping by stabilizing activity and retraining the body to function effectively (graded exercise, CBT), and (c) assist the patients in managing the social and financial aspects of their illness and where possible remaining in or returning to employment (problem solving).

General Measures

Providing Advice on Symptom Management

One of the most important interventions the clinician can make is to encourage and guide the person in the active self-management of his illness. Such advice will include the importance of being realistic about what one is able to accomplish, without giving up hope for improvement in the future. It should include information on the pros and cons of self-medication, particularly with analgesics, and might also require a discussion of the potential benefits and risks of iatrogenic harm from seeking treatment from other practitioners, conventional and alternative. The overall aim is to encourage the patients to feel that there are things that they can do to manage the condition themselves, to accept the reality of their illness while still planning positively for the future, and to be cautious about seeking potentially harmful and expensive treatments.

Managing Activity and Avoidance

Once activity is stabilized and large fluctuations between excessive rest and unsustainable activity reduced, gradual increases in activity can be advised. It is critical, however, to distinguish between carefully graded increases carried out in collaboration with the patient and a "forced" or over-ambitious exercise regimen.

Managing Occupational and Social Factors

Patients who continue working may be over-stressed by the effort of doing this. Those who have left work may have become inactive and demoralized and may not wish to return to the same job. These situations require a problem-solving approach to consider how to manage work demands, achieve a graded return to work, or plan an alternative career. Ongoing litigation is potentially a complicating factor, because it reinforces (and may reward) the patient for remaining symptomatic and disabled. A large trial in Canada that randomized patients either to litigation or to no fault

compensation for whiplash injury found that symptoms lasted longer in the former group [123].

Pharmacological Therapies

Antidepressants

Antidepressant drug treatment is indicated by the fact that (a) many patients with CFS have depressive and anxiety syndromes and (b) these agents reduce pain and improve sleep, even in the absence of depression. However, the evidence that antidepressants lead to an overall improvement in CFS is mixed [124].

Tricyclic antidepressants (TCAs) are probably more effective than selective serotonin reuptake inhibitors (SSRIs) for relieving pain [125] and for inducing sleep. Small doses (e.g., 25–50 mg/day of amitriptyline) are often adequate for these purposes.

SSRIs are generally better tolerated than TCAs. However, the very few available clinical trials have not been very encouraging for the treatment of CFS [126]. Venlafaxine, a dual serotonin and norepinephrine reuptake inhibitor (SNRI), is useful for pain and has been reported as showing initial promise in CFS [127]. Moclobemide, a reversible inhibitor of monoamine oxidase A, has been reported to be of no benefit in fibromyalgia, but of some value in increasing energy in CFS [128].

Other Pharmacological Agents

Analgesics, including opiates, are occasionally used for pain in CFS and related conditions, especially fibromyalgia. However, there are no trials of their use, and a major concern about the development of dependence. As with opiates, great caution is required with benzodiazepines, because of the risk of dependence in patients with chronic conditions. TCAs are probably preferable to treat insomnia, and the chronic use of benzodiazepines should be reserved for cases with intractable anxiety.

Given the finding of low serum cortisol, it is not surprising that corticosteroids have been tried. Hydrocortisone was reported to produce some benefit in CFS, but was not recommended because of the long-term risks of adrenal suppression [129]. Fludrocortisone has been used in CFS patients with orthostatic hypotension, but has been found to be of no value [130].

Amphetamines have been tried in CFS with some evidence of short-term efficacy [131], but are not widely used because of the risk of dependence and are not recommended.

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Summary

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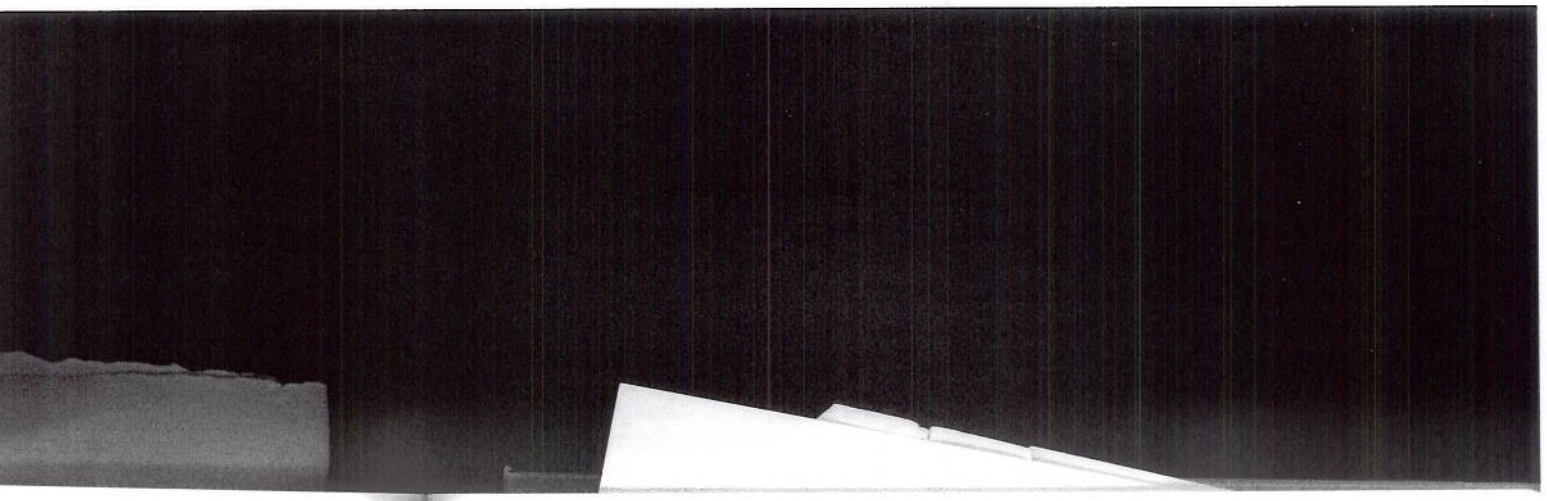

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Numerous other agents have also been tried in CFS. These include central nervous agents such as galanthamine, vitamins such as B12, alternative approaches such as homeopathy, antiviral agents including acyclovir, immunological therapies such as immunoglobulins, and many others. None can yet be recommended [132].

Summary

It is wise to exercise caution when prescribing in CFS. The mainstay of therapy continues to be antidepressant drugs, which may be helpful for mood, pain, and sleep, but have limited effect on overall outcome. TCAs are preferred for night sedation and pain, but greater tolerability may mean that an SSRI or an SNRI is preferable as first-line treatment. In current clinical practice, patients often receive low doses of antidepressants, but higher doses may be required to achieve a therapeutic response in some patients. The increased interest in pharmacological treatment of functional syndromes in the past few years will likely expand treatment options, and there are several new medications that show promise, including duloxetine, milnacipran, and pregabalin. However, the available evidence suggests that drug therapy has a limited role in the management of these conditions.

Specialist Non-Pharmacological Treatments

If the patient does not respond to or requires more active treatment than the general and pharmacological management described above, referral for specialist non-pharmacological therapy should be considered. For most patients, a rehabilitative outpatient programme based on appropriately managed increases in activity, either as graded exercise therapy or as CBT, is indicated. Some patients may require inpatient multidisciplinary rehabilitation, but at present there is inadequate evidence of its efficacy [133].

Graded Exercise Therapy

This is a structured progressive exercise programme administered and carefully monitored by an exercise therapist. It may be given in individual or group form, but the evidence is best for individually administered treatment [134].

Graded exercise therapy follows the basic principles of exercise prescription for healthy individuals, adapted to the patient's current capacity. The initial exercise intensity and duration are determined on an individual basis, and may be done using heart rate monitoring. Most patients can begin at an intensity of 40% of their maximum aerobic capacity, which approximately

equates to 50% of their estimated individual heart rate reserve added to their resting heart rate (e.g., if the maximum heart rate is 180 beats per minute (bpm) and the resting heart rate is 80 bpm, the heart rate reserve is 100 bpm and the exercise target heart rate is $80 + (0.5 \times 100) = 130$ bpm). This heart rate should not be exceeded; if it does, the patients should stop exercising for one or two minutes and then resume. Patients who are very disabled, or who have extremely low exercise tolerance, may be better to begin with two weeks of stretching alone without aerobic activity, and then to adopt alternate day aerobic exercise, before building up frequency, duration, and then intensity. The important principle is to calculate exercise capacity conservatively to start with, as well as ensuring agreement to try what is proposed.

At each clinic visit, joint planning of the following one or two weeks' exercise prescription is completed. The initial aim is to establish a regular pattern of exercise (usually walking), with exercise 5 days per week. Home exercise sessions should initially last between 5 and 15 minutes, depending on ability and exercise tolerance. The duration is increased by 1 or 2 minutes per week up to a maximum 30 minutes per homework session. Then the intensity of exercise can be increased to a target heart rate of 60% and then 70% of their heart rate reserve added to their resting heart rate. Patients will respond differently: some will take a lot longer to adapt to each new level, whereas others will have to be held back, particularly those who have been active sports participants in the past. Those patients who are inclined to over-exert themselves in an attempt to speed up the recovery process should be monitored carefully, as this can be a contributing factor in non-recovery or relapse.

Graded exercise therapy has been found in a systematic review to be of benefit in both CFS and fibromyalgia. In fibromyalgia, four high-quality aerobic training studies reported significantly greater improvements in pain with exercise than with comparison treatments [135], whilst in CFS, four high-quality trials all found benefits over comparison treatments in symptoms and disability [136]. There were, however, substantial numbers of dropouts in one study. Of particular interest is a trial of brief simple education about the physiology and rationale of exercise that found it to be as effective as CBT [137]. The Australian immunologist Andrew Lloyd reviewed all the evidence in an editorial entitled "To exercise or not to exercise in chronic fatigue syndrome? No longer a question" [138]. However, if we were to judge only by patient confidence in the intervention and anecdotal evidence of possible ill effects from apparently hasty and amateurish programmes, we would have to conclude that it remains very much a question.

Cognitive-Behavioural Therapy (CBT)

There are a variety of types of CBT. Here we refer to a collaborative psychologically informed type of rehabilitation that aims to achieve both graded

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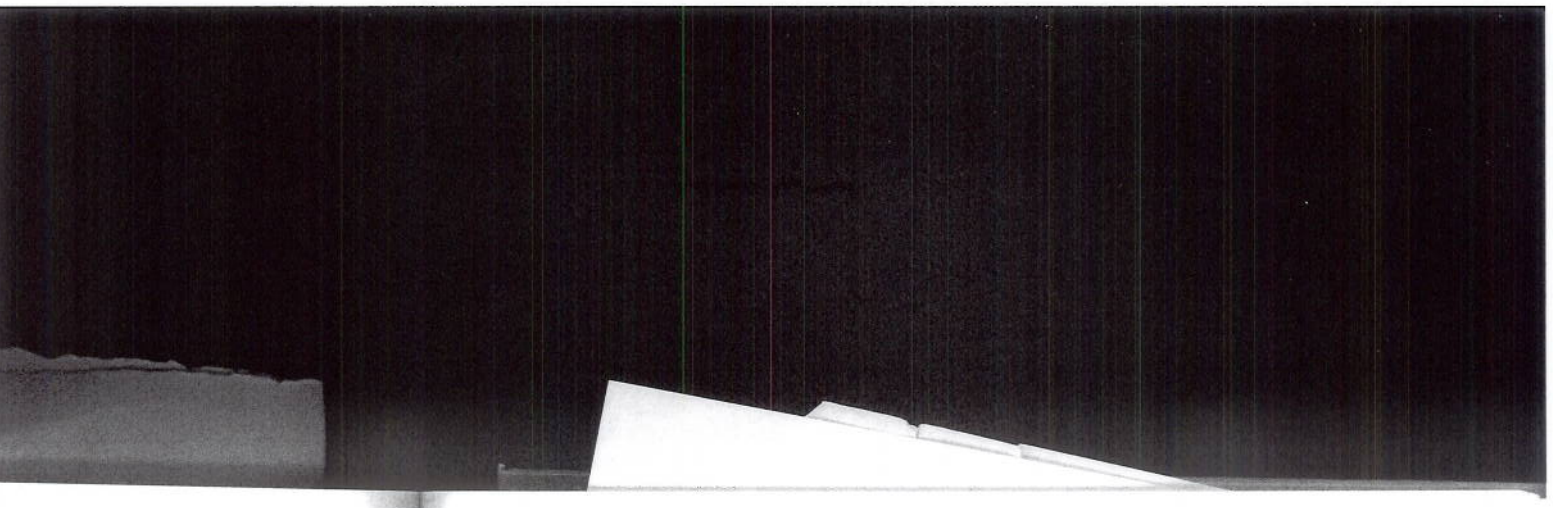

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increases in activity and changes in unhelpful beliefs and concerns about symptoms. It may also include problem solving for life and occupational dilemmas. It can be given in an individual or group form, although there is more evidence for the efficacy of individual therapy [139].

The procedure includes: (a) non-judgmentally eliciting the patients' own illness model, appraisal of situation, and the ways to cope; (b) introducing the possibility of alternatives; (c) helping the patient choose which beliefs and coping behaviours are most helpful by conducting behavioural experiments. The key question for the behavioural experiment is: "Is it possible for me to make changes in my behaviour that will allow me to achieve my goals?" The patient is encouraged to think of the illness as "real but reversible by his or her own efforts" rather than (as many patients do) as a fixed unalterable disease. Their ability to make changes is a test of these alternative hypotheses. The aim of behavioural change is to increase activity and to achieve specific goals. Problem solving is used to address relevant occupational and interpersonal difficulties. A typical therapy takes place over 14 sessions. The duration of each session is initially 90 minutes, then 50 minutes. The first four sessions are weekly; the subsequent ones bi-weekly over 5 months.

In CFS, individually administered CBT has been found to be effective in two systematic reviews, with approximately two-thirds of patients showing significant improvement. Three high-quality trials (total 164 patients) found improvement in both symptoms and disability and concluded that CBT appears to be an effective and acceptable treatment for adult outpatients with CFS [132, 140]. However, CBT remains a skilled treatment that not everyone is qualified to deliver: Dutch general practitioners were unable to perform it for CFS patients [141].

Patients Who Do Not Respond to Treatment

Most patients respond to some degree to rehabilitative therapies, but many will only achieve partial improvement and some will fail to improve at all. In such cases, the management is the same as that for other chronic conditions: to maximize functioning and quality of life while minimizing the risk of iatrogenic harm. While it is desirable that all patients should have a trial of rehabilitative treatment, a balance has to be struck between heroic efforts at therapy and acceptance of chronic illness. Many physicians are reluctant to accept chronic disability in these patients, perhaps because they do not regard these conditions as true diseases. Pushing patients beyond their capabilities may only demoralize them, or cause them to retreat further into invalidism. For such patients, regular follow-up from a single physician is often the best treatment.

SUMMARY

Consistent Evidence

CFS is not a new condition. Both CFS and neurasthenia can be reliably diagnosed using well-defined epidemiological criteria. The core symptom in CFS is excessive mental and physical fatigue, made worse by minor mental or physical activity, and not readily relieved by rest. Sleep is rarely normal.

There are substantial overlaps between CFS and neurasthenia: virtually everyone who fulfils criteria for the former will fulfil criteria for the latter. There is considerable overlap between CFS, neurasthenia, and other unexplained syndromes such as fibromyalgia. In the English-speaking world, CFS is often called myalgic encephalomyelitis.

There is overlap between CFS, neurasthenia, and common psychiatric disorders, mainly depression and anxiety. Such comorbidity is more pronounced in specialist centres.

CFS affects all age groups, but is very uncommon before puberty. It is commoner in females, especially in specialist settings. Contrary to popular belief, neither CFS nor neurasthenia is commoner in upper social classes. CFS can be triggered by external stressors such as certain viral infections and/or life events. Some viral infections, most particularly Epstein–Barr virus infection, are more likely to trigger CFS than others. Vulnerability to these triggers is increased by a previous history of emotional disorders.

Patients seen in specialist settings in Western cultures with the label of CFS or its equivalents are often resistant to psychological labels and/or explanations.

Prolonged rest is not the treatment of choice for CFS.

Incomplete Evidence

Although both CFS and neurasthenia can be reliably diagnosed, their nosological status is uncertain.

The origin of the profound physical and mental fatigue in CFS is fundamentally unknown, but it is more likely to reflect central rather than peripheral processes. It is unlikely that there is a primary neuromuscular origin to symptoms: observed abnormalities in the peripheral muscles are more likely to be secondary rather than primary.

There is some evidence that particular personality types, such as perfectionism, increase the risk of CFS, but this is not established beyond doubt. Early deprivation/abuse is often reported in clinical populations, but whether this is a genuine risk factor or the result of selection or recall bias remains unclear.

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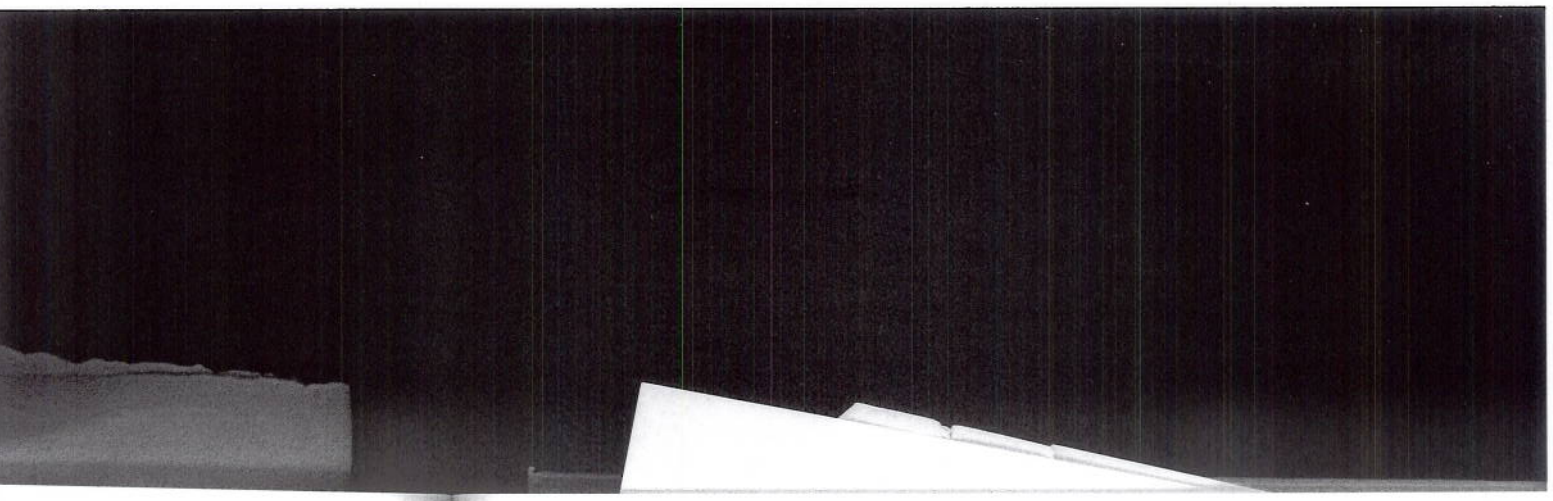

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There is increasing evidence of dysfunction of the hypothalamic-pituitary-adrenal axis in CFS: it is unknown how or if this is related to ill health, or is a consequence. The changes are not those seen in classic major depression. There is increasing evidence of mild immune activation in CFS: it is uncertain if this is a primary abnormality, or related to neuroendocrine changes. Orthostatic intolerance is reported in CFS populations, but it is unclear whether this is secondary, and how it relates to anxiety disorders.

Whilst some form of graded activity programme is the best current treatment, it is unclear how, when, and in what form this should be managed. The role, if any, of antidepressant therapy remains unclear.

The prognosis of CFS in specialist settings is poor, but it is unclear how much this reflects selection bias as opposed to the true natural history.

There is clear genetic predisposition, but what genes are involved, what is the nature of the genetic vulnerability, and how this relates to genetic vulnerability to depression or anxiety is unknown.

The cultural epidemiology of CFS and neurasthenia remains uncertain, but fatigue is universal. Why are there cultural variations, and what significance do they have?

Areas Still Open to Research

The issues still open to research are many. Among them: how some viral infections, such as Epstein–Barr virus infection, have a particular propensity to trigger CFS; the origin of the sex differences observed in epidemiological studies; the precise nature and role of sleep disturbance; the mechanism of fatigue; how rehabilitative treatment works; how or if CFS can be prevented.

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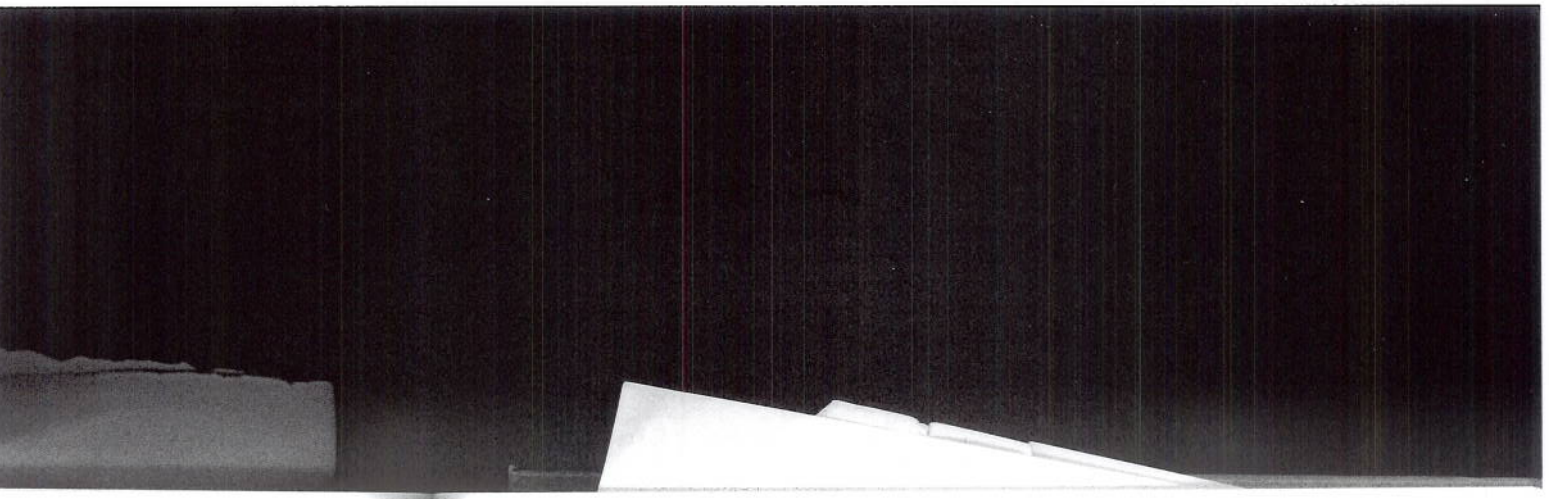

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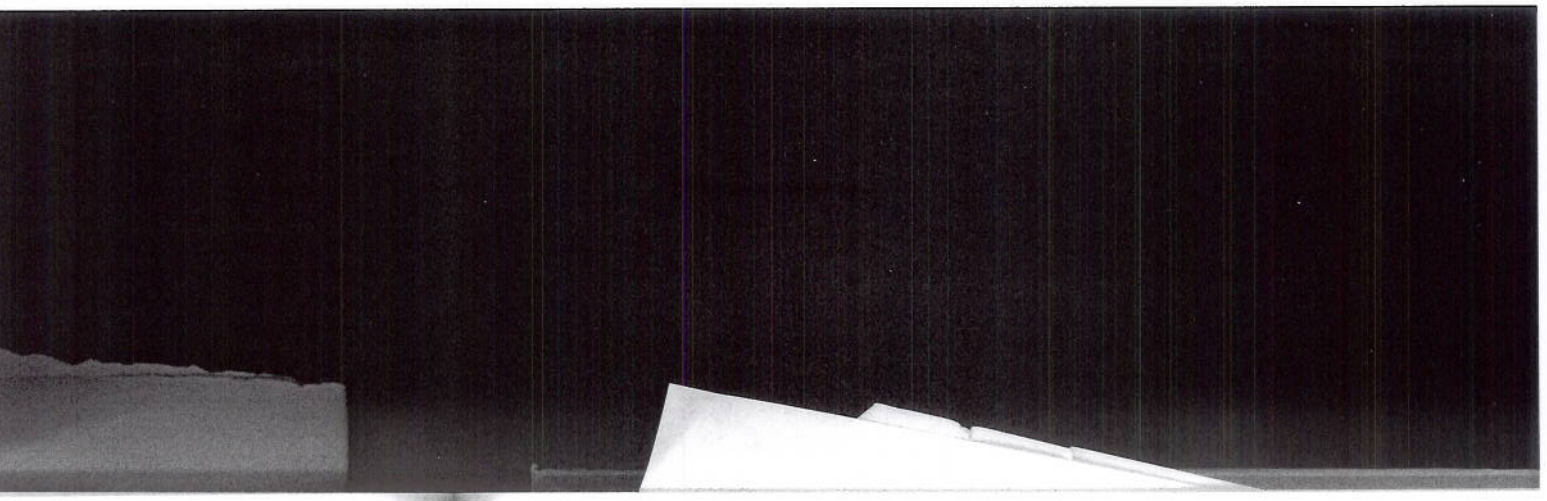

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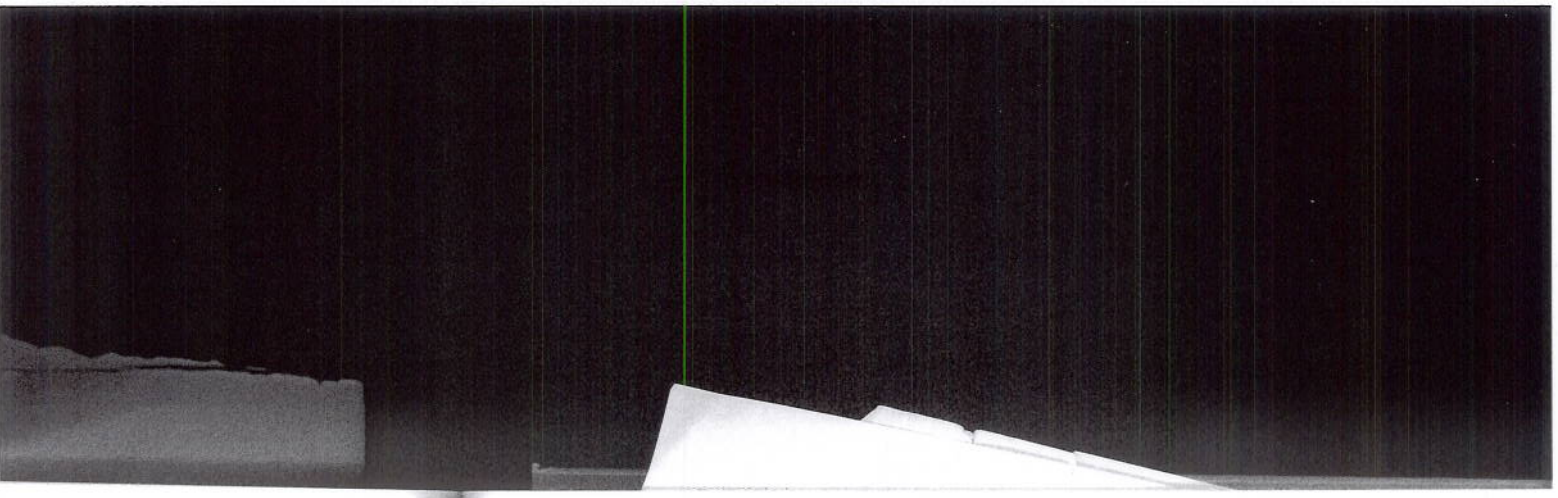

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From Neurasthenia

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