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Chronic fatigue syndrome

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"Chronic fatigue syndrome" (Sharpe *et al*, 1991) is an operational definition for conditions of disabling physical fatigue, of over six months duration, unexplained by primary physical or psychiatric causes. It encompasses nomenclature such as "myalgic encephalomyelitis" (Acheson, 1959), "post-viral fatigue syndrome" (Behan *et al*, 1985) and "chronic mononucleosis syndrome" (Straus, 1988).

History

Neurasthenia

Beard (1881) described the syndrome "neurasthenia", where decreased physical and mental energy were prominent complaints and which was thought to be of 'organic' aetiology. Nervous system disease, febrile illness and environmental factors (including wireless telegraphy) were implicated . It was commonly diagnosed in higher social classes. Interest in neurasthenia waned due to lack of diagnostic signs, a broad definition and increasing recognition of psychological factors in the condition (Wessely, 1990).

Royal Free disease, myalgic encephalomyelitis and post-viral (fatigue) syndrome

Interest was rekindled when the Royal Free epidemic (1955) debilitated medical and nursing staff. Signs and symptoms of this condition were inconsistent with then current knowledge of viral illness. A medical follow-up of sufferers showed that chronic disability occurred in a proportion (Ramsay, 1986), but a psychiatric follow-up suggested that psychological factors were important in disability. An overlap with epidemic hysteria was suggested, which helped to explain the rapid spread of the "illness", its predilection for medical and nursing staff (and not patients), and inconsistent clinical signs (McEvedy & Beard, 1973). However, similar cases of a sporadic nature were later reported.

Some suspected viral infection in the Royal Free disease and other similar cases worldwide. These were termed "benign myalgic encephalomyelitis" by Acheson (1959), a term later replaced by "myalgic encephalomyelitis" due to the chronicity of some cases.

Serological documentation of such cases later implicated several agents, so the more general term "post-viral (fatigue) syndrome" was advocated (Calder & Warnock, 1984; Behan & Behan, 1988). Research in the UK suggested exposure to enteroviruses, particularly Coxsackie B, as a risk factor. In the USA, Epstein-Barr virus (EBV) was implicated in a similar syndrome later termed "chronic mononucleosis syndrome" (Straus, 1988).

Chronic fatigue syndrome

Patients with identical clinical syndromes, but no documentation of preceding infection, were excluded from the definitions outlined above. This was felt to be unsatisfactory by researchers who introduced the term "chronic fatigue syndrome" (CFS) (Holmes *et al*, 1988). This term had no aetiological assumptions in the case definition, and gave clear operational criteria. Patients with chronic mononucleosis, post-viral fatigue syndrome, "ME" (myalgic encephalomyelitis) or with identical syndromes (but no proven infection) would be included. The criteria were criticised for excluding concurrent psychiatric morbidity, which might be reactive to fatigue rather than causative. One study of chronically fatigued patients found only 5% met these criteria, most being excluded because of concurrent psychiatric symptomatology (Manu *et al*, 1988).

CFS criteria introduced in Australia (Lloyd *et al*, 1988) would include patients with concurrent psychiatric symptoms (if these did not explain fatigue), but criteria added which required the demonstration of immune abnormalities (this

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needing specialised facilities and of unproven value) were criticised (David *et al*, 1988).

The consensus criteria for CFS ("Oxford criteria") were devised in the UK. They do not require demonstration of immune abnormalities and allow some concurrent psychiatric symptoms. A narrower subcategory of these criteria is favoured by some – "post-infectious fatigue syndrome" (PIFS), which has the additional criteria of serological and clinical documentation of febrile illness preceding fatigue onset. These criteria (CFS and PIFS) are widely used in the UK.

Aetiology of CFS

A complex aetiological model is needed (David *et al*, 1988, 1991). Although theories are listed under physical and psychological causation, aetiology is probably multi-factorial.

Physical causation

Persistent viral infection

Enteroviruses. A raised titre of anti-Coxsackie B Igm was found in sufferers, relative to the general population, and an association was detected between Coxsackie B outbreaks and post-viral fatigue syndrome cases (Calder *et al*, 1987; Behan & Behan, 1988). The VP1 antigen, common to enteroviruses, was identified and a test developed to screen for recent enterovirus infection. This would help decide whether to screen for Coxsackie. In one study the majority of post-viral fatigue syndrome patients were VP1 positive and had evidence of persistent enteroviral infection (Yousef *et al*, 1988). The VP1 test became known as the ME test and a standard screening investigation, but overlap was found with neuromuscular disease (Halpin & Wessely, 1989) and depression (Lynch & Seth, 1989).

Epstein-Barr virus (EBV). Longitudinal studies of patients with "chronic mononucleosis syndrome", believed due to chronic Epstein-Barr virus (EBV) infection, found no relationship between anti-EBV titres and clinical outcome (Gold *et al*, 1990). Other pathogens have since been implicated with no consistent evidence, but are not discussed here.

Muscle dysfunction

Persistent muscle infection by enteroviruses (Cunningham *et al*, 1992) and post-infective damage to muscle fibres (Behan & Behan, 1988) and mitochondria have been reported. One NMR spectroscopy study showed abnormal intracellular acidosis associated with exercise, but was not replicated (Yonge, 1988). The muscle fibre damage reported in biopsies could be explained by prolonged inactivity. Evidence of persistent muscle infection is weak. Muscle function is consistently normal on ergometric and physiological testing (Lloyd *et al*, 1988*a*; Stokes *et al*, 1988).

Box 1. Post-infectious fatigue syndrome (PIFS) (Sharpe *et al*, 1991)

This is a subtype of CFS which either follows an infection or is associated with a current infection (although whether such associated infection is of aetiological significance is a topic for research). To meet research criteria for PIFS, patients must fulfil both the criteria for CFS and the additional criteria:

1. **There is a definite evidence of infection at onset or presentation (a patient's self-report is unlikely to be sufficiently reliable).**
2. **The syndrome is present for a minimum of six months after onset of infection**
3. **The infection has been corroborated by laboratory evidence**

Immune dysfunction

Abnormal immune responses might be implicated in CFS, with reduced or enhanced responses after normally minor infections. After acute infection, immune depression can lead to a cycle of chronic infection and fatigue (Klimas *et al*, 1990); or a heightened, prolonged immune activation may produce excess leukotrines (humoral products) which have metabolic, endocrine and neuropsychiatric effects as well as immune effects (MacDonald *et al*, 1987; Linde *et al*, 1992). However, immune changes occur in conditions such as depressive illnesses (of all severity) and this factor has yet to be satisfactorily accounted for in research in CFS.

Electrolyte imbalance

A controlled study reported low intracellular magnesium in CFS patients and improvement in fatigue and mood with rectification by intramuscular magnesium injections (Cox *et al*,

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1991). The finding of low intracellular magnesium was not replicated in other CFS patients.

Chronic candidiasis
Some groups of patients believe that chronic intestinal overgrowth of *Candida albicans* produces fatigue via toxins or allergic response. In a double-blind, placebo controlled study of CFS patients, antifungal agents were found to be ineffective.

Psychological causation

The Royal Free follow-up confirmed substantial psychiatric morbidity (McEvedy & Beard, 1973) as did a study of post-viral fatigue syndrome (Behan & Behan, 1988) and of epidemic neuromyasthenia (Taerk *et al*,1987). In these studies depressive illness was the major psychiatric diagnosis. Some researchers viewed depressive symptoms as "reactive" to disability or "neuropsychiatric" due to disturbed brain function (Behan & Behan, 1988); others viewed these symptoms as of primary aetiological importance, while some proposed that viral infection produced an affective disorder in predisposed individuals (Taerk *et al*, 1987).

Depression ?
If CFS is a CNS disorder (distinct from depression), its rates of psychiatric morbidity should be similar to CNS disorders such as epilepsy and multiple sclerosis (MS). However, hospital-based studies show over 50% of CFS patients as meeting diagnostic criteria for major depression, which is a higher rate than expected in epilepsy or MS (David *et al*, 1991). Even if depressive symptoms in CFS are proved to be reactive, if these are untreated they can become chronic and disabling. They can affect motivation, increase awareness of fatigue and affect all areas of function.

Anxiety ?
Anxiety symptoms may occur separately from depressive symptoms, but have not been as rigorously studied. They were documented by McEvedy & Beard (1973) in the Royal Free follow-up and are consistent with the concept of epidemic hysteria where anxiety is translated into physical symptoms by conversion. Epidemic hysteria is no longer seriously suggested as a major cause of CFS, but chronic hyperventilation has been implicated. This can produce (often atypical) somatic symptoms; patients may be unaware of the anxiety symptoms driving hyperventilation, or even of the hyperventilation itself (Rosen *et al*, 1990).

Assessment and investigation

Psychiatrists may feel anxiety as to the uncertain nature of fatigue in CFS, which has a wide differential diagnosis, and this may be communicated to the patient. Additional pressures are the publicity associated with CFS and the questioning of the role of psychiatric treatment by some of the medical profession (and the patients' organisations).

Medical assessment

An experienced physician should have excluded common causes of fatigue, investigations being based on clinical findings rather than being routine (David *et al*, 1991). Further investigation may be warranted by any significant new signs or symptoms. Some patients later turn out to have undiagnosed physical pathology, but available evidence suggests that this is a small number. Investigations should be organised by a key physician to help continuity, and to counter pressure (from anxious patients or relatives) for unnecessary investigation or referral. Effective communication is essential between the psychiatrist, physician and general practitioner.

Box 2. Characteristics of chronic fatigue syndrome (CFS) (Sharpe *et al*, 1991)

1. **Fatigue is the principal symptom**
2. **A definite onset, and a duration that is not life-long**
3. **The fatigue is severe and disabling, and affects physical and mental functioning**
4. **The fatigue is present for a minimum of six months, and present for at least 50% of that time**
5. **Other symptoms may be present, particularly myalgia, mood and sleep disturbance**
6. **Exclusions: people with medical conditions known to cause chronic fatigue, and those with a current diagnosis of schizophrenia, manic depressive illness, substance misuse, eating disorder or proven organic brain disease.**
7. **Other psychiatric disorders (including depressive illness, anxiety disorders, and hyperventilation syndrome) are not necessarily reasons for exclusion**

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Psychiatric assessment

A major difficulty in assessment may be that psychiatric consultation is delayed, so that information may be biased by "effort after meaning" (related to attribution), and selective recall. Available notes should be reviewed and the referral discussed with the physician (as investigations may be pending); background information from the patient's GP may be useful as they are likely to have had longer and more detailed acquaintance with the patient.

The onset and evolution of the fatigue and psychiatric symptoms may be important. If psychiatric symptoms pre-date fatigue they could help explain it, so the CFS criteria are not met. A simultaneous onset of psychiatric and fatigue symptoms does not automatically exclude patients from CFS criteria, but primary psychiatric disorders may need to be carefully considered. A delay between the onset of fatigue and psychiatric symptoms is often seen in patients meeting the criteria.

Psychiatric diagnoses included under CFS criteria

Psychiatric conditions specifically excluded from the CFS criteria are schizophrenia (and other psychoses), manic depressive illness, eating disorders, substance misuse and organic psychosyndromes (both acute and chronic). Depressive illness and anxiety-related disorders are not necessarily reasons for exclusion.

Major depression

Seventy to eighty per cent of CFS patients in hospital studies are psychiatric cases, and over 50% meet DSM–III criteria for major depression (David *et al*, 1991). Phenomenological differences between CFS patients with major depression and "typical" depressives are that CFS patients have less sleep and appetite reduction, and lowered self-esteem (Powell *et al*, 1990). Lassitude and concentration disturbance occur in both CFS cases and non-cases. Some suggest disregarding these to reduce overdiagnosis. If an atypical depression model of CFS is used, underdiagnosis could also be a risk, as a restricted range of affective symptoms may be expressed, with some somatised as fatigue.

Suicide risk assessment should be conventional. Caution is advised as patients may not disclose suicidal intent if they are reluctant to admit psychiatric symptoms. The suicide rate peculiar to CFS is not yet established.

Anxiety-related disorders

Other diagnostic difficulties are seen,for example somatic complaints in CFS may overlap with anxiety symptoms. Muscle pain with an organic basis may lead to arousal, then superimposed anxiety symptoms such as generalised muscle tension, muscle weakness,and paraesthesiae. Clues that symptoms are anxiety-related may come from impression at interview, the symptoms being clearly stress-related, or not worsening when fatigue worsens.

Box 3. Definition of chronic fatigue syndrome (as modified by Lloyd *et al*, 1988*b*): At least six months chronic, persistent or relapsing fatigue of a generalised nature, causing major disruption of usual daily activities. Two major criteria or one major and three minor criteria are necessary:

1 **Symptoms: At least six months continuously or relapsing on three or more occasions over at least six months:**
Major:Concentration/memory impairment
Minor:Myalgia, arthralgia, depression, tinnitus, paraesthesiae, headaches.
2 **Signs: Present at least once after start of illness:**
Major: Lymphadenopathy
Minor: Pharyngitis,muscle tenderness
3 **Immunology:**
Major:Cutaneous anergy, T4 or T8 lymphopaenia
Minor: Hypoergy

Assessment of symptom severity

Well-validated, self-rated scales for depression such the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983), and the Beck Depression Inventory (BDI) (Beck *et al*, 1961) are useful, but may not detect somatised symptoms. Interview-rated assessment of depression and anxiety should be by established scales such as the Hamilton Scales or Montgomery Åsberg Depression Rating Scale using conventional rating instructions.

Fatigue self-rating scales of visual analog and Likert type have been devised. The Fatigue Questionnaire (Wessely *et al*, 1989) measures mental and physical fatigue, is brief, and has been validated in hospital and the community. Interview ratings of fatigue are largely research

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tools and have disadvantages of bias, and use of interviewer time, but can assess fatigue in greater depth.

Management of CFS

Physical treatment

Antidepressants

Some psychiatrists use antidepressants for the treatment of specific symptoms in CFS, for example fatigue, sleep disturbance, and myalgic symptoms, even if depressive symptoms are very mild or absent. There are no published, randomised controlled studies clearly demonstrating the benefit of antidepressant therapy in CFS patients with depressive symptoms, let alone patients without obvious depressive symptoms.

It is recommended that treatment with antidepressants is guided by the severity of depressive symptoms, i.e. in patients with both CFS and major depression and not routinely used in all CFS patients (Lynch *et al*, 1991). The potential for antidepressant toxicity in overdose and their side-effects must be outweighed by clear benefits

CFS patients who also meet criteria for major depression commonly have depressive symptomatology of mild to moderate severity. Several factors influence which antidepressant is used:

(1) Prolonged inactivity increases the risk of autonomic side-effects such as postural hypotension
(2) Sedation might worsen mental and physical fatigue
(3) Patients may have concerns about medication, such as fear of being addicted or a worsening of symptoms.

Anxiolytics and hypnotics

Anxiety-related disorders occur in a substantial number of CFS patients as primary and secondary diagnoses. If mildly severe depressive symptoms co-exist it may be difficult to determine which are primary, and the best treatment. Antidepressants could be tried as they are effective against anxiety and depressive symptoms, but their potential toxicity in overdose and side-effects may make one consider alternative physical treatments such as the benzodiazepines, neuroleptics and novel anxiolytics (buspirone, zopiclone).

However, these anxiolytics and hypnotics may have their own disavantages. The risk of benzodiazepine dependence is high; neuroleptics may have risks of tardive dyskinesia and extrapyramidal side-effects.

Psychological treatment

The media tend to sensationalise or stigmatise CFS, a behaviour unfortunately mirrored in the medical profession. CFS patients may feel disbelieved and cling to beliefs of physical causation, such as viral infection, making them inaccessible to alternative explanations.

Faced with a patient demanding investigation, despite negative results and no apparent cause or improvement, the physician may suggest a psychiatric referral. Patients may have various reactions to this, usually negative, as they feel that they are not being believed. Behaviour that may result from these reactions includes minimising stressors and psychological problems, 'enforced' compliance to please referring physicians, and 'pseudo-psychologisation', where psychological factors are acknowledged in CFS in general, but not in their individual case.

Engaging the patient in treatment

The approaches used in patients with medically unexplained symptoms (somatisation) can be applied (Creed *et al*, 1993). Consultation is geared to how psychological factors maintain disability, rather than speculation on aetiology. One problem with communicating with patients is a dualistic view that illnesses are wholly physical (and real, as they can be objectively assessed) or psychological (where they can not be, and are thus 'imagined'). Patients must know that their suffering is believed, and that depression and anxiety are "real" symptoms, that can alter subjective awareness of somatic complaints and affect disability.

Patient expectations should be realistic. They should know that treatment will help improve function and fatigue but may not "cure". It is important to explain why no definite cause for the fatigue was found, and the possible combination of causes for it. For example:

(1) It may be multifactorial, e.g. stress, viral infection, poor diet interact
(2) Investigations may not be sensitive enough to detect certain causes
(3) One factor provoked fatigue, e.g. a viral infection and another maintained it, e.g. reaction to disability

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Supportive psychotherapy

This therapy may be used where patients are not suited to or do not wish to use other forms of psychotherapy. No specific causation theory of CFS is necessary. Advice is given where appropriate and the patient encouraged to use existing coping strategies. Change is not intended and interpretations are not usually given. Sessions may be fortnightly, for up to six months.

Interpersonal psychotherapy

This model could be applied where secondary losses have occurred in CFS. Strategies used include assessment of the key elements of particular loss areas and a plan to find alternatives to some of these. For example a responsible career job may not be replaced but different roles may be found, initially with responsibilities appropriate to the patient's capacity after recovery. In CFS, role change, loss of independence and change in relationships (due to illness) are key areas.

Focal psychodynamic psychotherapy

Patients with chronic conditions such as irritable bowel syndrome have benefited from this approach (Guthrie *et al*, 1991). In CFS, the doctor–patient relationship may be damaged and patients may be unable to express their emotional experience of illness. The aim is to foster a confiding therapeutic relationship, and the focus is on areas that may be maintaining disability, such as doctor–patient communication, adjustment to illness, blocking feelings and expressing distress in physical symptoms. Transference is addressed where relevant. Weekly one-hour sessions for about six months would be appropriate.

Cognitive–behavioural therapy

This has developed from work in chronic pain programmes (Phillips, 1987), focusing on changing attributions of illness causation with a graded increase in activity. Cognitive theory can be applied to depression, anxiety, pain and somatisation, all of which can occur in CFS, so there are many possible approaches. Experience suggests that attributions of illness causation should be prioritised.

At initial assessment, the therapist should emphasise the damaging effect that inappropriate investigation and referrals during treatment can have. The patient should agree that investigations should be co-ordinated by one physician. Patients must be:

(1) Able to identify automatic thought patterns
(2) Motivated to change both thinking patterns and behaviour
(3) Free from severe depression. The patient may be inaccesible due to depressive symptoms, and misjudged treatment could precipitate a suicide attempt.

Pitfalls that may arise in assessing motivation may be that the patient has an undisclosed secondary gain in maintaining the sick role; is simply 'going through the motions' with psychiatric treatment to appease their physician; and that targeted activities are not as valued as appeared (ambivalence).

Goals must be agreed upon, such as challenging underlying anxiety-provoking thought patterns on attempting particular activities. The activity can then be increased at a mutually agreed rate. Treatment takes between 10 and 20 sessions.

As cognitive therapy is self-directed, patients keep a diary in which they assess automatic thought patterns, behaviour and confidence in performing the activity ("mastery and pleasure"). They should take an increasingly active role in monitoring cognitions and altering behaviour as treatment progresses. Sometimes "refresher" sessions may be needed to maintain these skills.

Example of the cognitive therapy approach

Examples of cognitions:

Before activity

1 'I will feel tired if I do'

*2 'I feel tired, I must be doing too much'

3 'I am scared I will have a relapse if I do too much'

After activity

1 'My muscles are aching – the virus is flaring up again'

2 'I feel short of breath, my heart is pounding and I feel weak, I am sweaty and feverish'

Examples of intervention

*2 'I may be feeling more tired because I have not done as much of this activity recently'

'If I do more of this activity I will be less tired in the future'

Graded activity programmes

Activity programmes focus on mental and physical activities, with the aim of improving the patient's self-efficacy in managing these. Some programmes assume that inactivity and subsequent changes maintain disability, while others do not have such specific hypotheses and concentrate on self-efficacy and individual adjustment to illness. The duration of the programme should take into account the patient's abilities and the difficulty of the goals.

Many CFS patients want some control over the length and structure of the programme. Patients may find that prioritising activity according to

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their available energy enables them to achieve more. This is a skill they can use later without the therapist and which enhances their self-esteem, by breaking the link between attempting activity and "inevitable" fatigue. Up to 12 half-hour sessions may be needed.

Exercise programmes

Graded exercise programmes are geared to incremental changes in exercise (energy, time, difficulty) or other activity. In CFS it is assumed that due to prolonged inactivity, muscle strength, autonomic responses and perception of exercise-related stimuli change. In addition, phobic avoidance occurs, due partly to these changes, and compounds disability.

Individual programmes are set with mutually agreed targets and rate of activity change, usually in a CBT framework. Patients exercise and gain understanding of exercise-related sensations under therapist supervision. Self-directed treatment techniques are strongly recommended.

Anxiety management techniques

The patient needs a full understanding of anxiety, time to practice techniques, and support from the therapist. Autogenic relaxation, imagery and progressive techniques (breathing and muscle control) can be used in CFS. The latter techniques are targeted on aberrant perception of somatic symptoms seen in chronic hyperventilation and myalgic symptoms.

Outcome of CFS

The follow-up studies in CFS suggest that conviction of physical causation of illness and chronic psychiatric morbidity predict poor outcome, but that outcome is generally better than previously believed. (Sharpe *et al*, 1993; Bonner *et al*, 1994)

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Multiple choice questions

1 The following are indicators of poor outcome in chronic fatigue syndrome (CFS):
- a The initial severity of the fatigue symptoms
- b Strong belief in a physical cause for the symptoms
- c The number of somatic complaints
- d The duration of the fatigue syndrome
- e The presence of long-lasting depressive symptoms

2 There is good evidence for the following in the development of CFS:
- a Life events of a "loss" type
- b Post-infective mitochondrial damage
- c Immune activation
- d Illness attribution
- e *Candida albicans* overgrowth in the intestine

3 In the assessment of a patient with possible CFS:
- a Severe depressive symptoms would strongly suggest an alternative diagnosis
- b Multiple sclerosis often presents with a clinically indistinguishable picture
- c The onset of depressive symptoms before fatigue may imply aetiological association
- d Patients must have over three months duration of symptoms to meet consensus criteria
- e VP1 antigen positivity is strongly suggestive of chronic viral infection

4 The following statements about these treatment approaches for CFS are true:
- a Graded activity approaches are less effective than graded exercise
- b Interpersonal therapy may be useful in patients who are unsuitable for cognitive behaviour therapy
- c Reattribution of illness belief is a core component of cognitive behaviour therapy
- d Graded exercise may worsen outcome if too rapid and intensive a programme is used
- e Cognitive behaviour therapy has a better outcome than antidepressant therapy

MCQ answers

1	2	3	4
a F	a F	a F	a F
b T	b F	b F	b T
c F	c F	c T	c T
d F	d T	d F	d F
e T	e F	e F	e F

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