CURRENT TOPIC

Chronic fatigue syndrome

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The media has shown some interest in children with chronic fatigue syndrome, although national coverage does not always accurately reflect the position of the current medical publications. For example, one television programme indicated that most adolescents with the illness might expect to be ill for at least four years, a suggestion that research papers do not confirm. It is thus prudent to consider what current research tells us, particularly when there is an apparent disparity of views about the illness between parents, support groups, and professionals.

An editorial in the *British Medical Journal*¹ and a report from the joint working group of the Royal Colleges of Physicians, Psychiatrists and General Practitioners² both called for more work to be carried out on the assessment and management of children and adolescents with chronic fatigue syndrome. This review seeks to delineate our knowledge from published work as it currently stands and suggests an important area of further work.

Nomenclature and definition

Many terms have been used over the years for illnesses involving severe and prolonged fatigue. In the middle of the 19th century the term neurasthenia was used.³ It was believed that neurasthenia was a form of "nervous exhaustion" brought about by an injury to the nervous system. The treatment advised was rest, and a term apparently given to such people was "sofa cases".⁴ Similar euphemisms exist today. Such terms as "skiver's sickness" and the term "yuppie flu" have been used, although there is no evidence to suggest a clear socioeconomic correlation.² Many other disorders described and defined over the years have much in common. They include fibromyalgia,⁵ myasthenia,⁶ neuromyasthenia,⁷ myalgic encephalomyelitis (ME),⁸ postviral fatigue syndrome,⁹ idiopathic chronic fatigue and myalgic syndrome,¹⁰ Iceland disease,¹¹ Royal Free disease,¹² chronic Epstein-Barr virus (EBV) infection,¹³ chronic infectious mononucleosis,¹⁴ benign ME,^{15 16} and postviral epidemic neuromyasthenia.⁷ The view that too much energy has been spent on nomenclature and too little on symptomatology and management is easy to see.¹⁷ Difficulties with nomenclature, however, reflect problems in coming to a common understanding of aetiology, natural history, and management. The joint college report considers chronic fatigue syndrome to

be the most helpful name² and attempts to take a few strides towards a more common understanding, although it concentrates mainly on adult sufferers.

Chronic fatigue syndrome was defined by the Centers for Disease Control and Prevention (CDC) in the USA to establish uniformity of diagnosis, primarily for research purposes.¹⁸ When originally defined in 1988, the CDC criteria specified that for a diagnosis to be made, two major criteria should be fulfilled:

- **debilitating fatigue reducing activity to less than 50% of the patient's premorbid activity for at least six months; and**
- **symptoms not explained by other medical or chronic psychiatric illness.**

In addition, the following minor criteria should be fulfilled:

- at least six *symptom* criteria; and
- at least two *physical* criteria or, failing that, at least eight *symptom* criteria.

SYMPTOM CRITERIA

- **sore throat**
- **painful cervical or axillary lymphadenopathy**
- **muscle discomfort or pain**
- **prolonged generalised fatigue after usual levels of activity**
- **headaches**
- **arthralgias (without swelling or redness)**
- **neuropsychological disorders such as photophobia, scotomata, forgetfulness, irritability, confusion, lack of concentration, or depression**
- **sleep disturbance (unrefreshing)**
- main symptom complex developing within a few days
- mild fever to 38.6°C or chills
- generalised muscle weakness.

PHYSICAL CRITERIA

- low grade fever corroborated by clinician
- non-exudative pharyngitis
- palpable axillary or cervical lymph nodes.

There has been some criticism of aspects of these criteria. For example, Dale and Straus¹⁹ pointed out that some psychiatric illnesses could be secondary to prolonged fatigue and that the CDC criteria did not clearly define when psychiatric illness is an exclusion criteria or when it is one of the neuropsychological symptom criteria. They suggested excluding only the group that had a chronic ongoing psychiatric illness that preceded the development of chronic fatigue. Criteria have been suggested

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by other workers in Australia^{20, 21} and the UK²² (the Oxford criteria). All the various definitions have been criticised^{23–25} and research continues in this area.

The CDC criteria have now been updated.²⁶ Specifically, this involved dropping all the physical signs from the inclusion criteria (that is, the physical criteria) and reducing the list of symptom criteria from 11 to eight by removing fever, rapid onset of symptoms, and generalised muscle weakness (which already appeared in the two major criteria). The neuropsychological disorders were restricted to problems with memory or concentration, and sleep disturbance was modified to “unrefreshing” sleep. The required number of symptoms for diagnosis was reduced to four from eight. The presence of non-psychotic depression no longer precluded the diagnosis of chronic fatigue syndrome (**changes in bold**).

There are specific criticisms of the use of the CDC criteria in children. Some workers have rightly pointed out that the illness behaviours of children may be significantly influenced by parental expectations and responses.²⁷ The CDC criteria, which require six months of fatigue for the diagnosis to be made in adults, may be too long for children.^{28, 29} Some childhood studies have selected cases based on six months or more of fatigue,^{30, 31} whereas others have used shorter durations such as two months²⁸ or six weeks³²; three months has been suggested by the joint colleges working party.² These shorter thresholds are justified on the basis that prolonged fatigue in children needs identifying earlier because of the greater sensitivity of children to the consequences from a developmental perspective.

As approximately 15% of referrals to paediatric infectious diseases clinics may involve youngsters with chronic, persistent fatigue,²⁸ it seems important to have a common understanding of the ways in which such illnesses may be defined. This is why, despite the disagreements, it is important to continue the research and debate in this area.

Aetiology

Many workers have investigated factors associated with chronic fatigue syndrome in the search for a clearer understanding of aetiology. A small number of patients with acute EBV infection may go on to develop long term fatigue,^{28, 32, 33} but this does not account for the volume of cases presenting with chronic fatigue syndrome, many of whom have no serological evidence of EBV infection. About 10–15% of children referred to specialist clinics have been found to have evidence of current or recent EBV infection.^{29, 34} Infections may play a part in ongoing symptomatology in a minority of patients,^{31, 35} but most of the agents (other than EBV) proposed, such as rubella, enteroviruses, herpesviruses (such as HHV6), and retroviruses (such as HTLV-II) have not been found to be important in subsequent research in that the methodology has been shown to be unsound or the finding has not been replicated.^{2, 19, 29, 36} The finding that enteroviral

RNA has been discovered in muscle biopsy material of some patients³⁷ has not been significant when case controlled designs have been used.^{38, 39}

Most of this research has been with adult patients. The evidence does not indicate chronic viral infection as the cause of ongoing prolonged fatigue, although the evidence of a viral precipitant to chronic fatigue syndrome is more widely accepted.² The infective argument (as an ongoing cause) is difficult to sustain in the absence of consistent and persistent infective markers.

The study of affected adults suggests that the fatigue is not local to the muscles, but is centrally mediated,⁴⁰ and this is concordant with the finding that mental fatigue is often coexistent with reported muscular fatigue.³⁰ There have been several biological findings in adults, including problems with red cell function, muscle function, T cell function, suppressor cell function, monocyte function, killer cell function, abnormal cytokine production, and high serum concentrations of chlorinated hydrocarbons, but their interpretation has been difficult.^{34, 35, 37, 41–47} There is some evidence for impaired functioning of the hypothalamic–pituitary–adrenal axis, but again whether this is primary is not clear.⁴¹ Similarly, the finding that there is hypoperfusion of the brain in chronic fatigue syndrome does not exclude excessive rest and inactivity as a cause, and so it is difficult to interpret.⁴⁸ Findings have often not been replicated^{2, 34} or have not involved controls, and some commentators have sought to explain the findings as arising from inactivity, under use, malnourishment, or coexisting infection,^{32, 36} rather than primary neuromuscular dysfunction. There is considerable evidence to support this view.

Studies show that prolonged rest affects “virtually every physiological system”.⁴⁹ A period of as little as one week can result in a measurable loss of muscle volume,⁵⁰ and four to six weeks of rest can result in up to 40% loss of muscle strength.⁵¹ In addition, the oxidative enzyme content, responsible for the production of energy, is severely affected by disuse.⁵² Mitochondrial function is adversely affected,⁵³ myosin ATP activity is reduced significantly in both type I and type II fibres,⁵⁴ muscle protein synthesis is reduced, and there is an increase in connective tissue.⁵² Research also shows changes in neural functioning after five weeks of bed rest, with reductions in local electromyographic activity and central activation.⁵⁵ The neural changes appear to recover more quickly than the contractile deficits, which may take at least 10 weeks to recover.

Studies have also shown that prolonged bed rest results in significant decrements in bone mineral density and that these take more than six months of normal activity to return to normal.⁵¹ There are also immunological consequences, such as a significant effect on T lymphocyte function.⁵⁶ It only takes 10 days of bed rest for the basal metabolic rate to reduce significantly, even during adequate nutritional intake.⁵⁷

Exercise after this period, with these clear deficits in muscle function, neural function, and energy producing capacity, will lead to exhaustion as the body struggles to cope and make adequate energy levels available. As well as being physically challenging with actual fatigue, it may be psychologically damaging. If physiological mechanisms are not understood, all the symptoms, with ongoing fatigue after exercise, may sustain a belief in serious illness. The response of excessive rest leads to a worsening of symptoms, both perceived and actual. In other words, if we wanted to produce an effect where a child was rendered wasted, fatigued, exhausted, desocialised, and depressed, we might put them in bed for three months and prevent them from going to school, because the research evidence suggests that this would surely have such an effect.

Most of the studies exploring aetiology have not been performed in children and so it is not clear whether the findings should be accepted as relevant to children as well as adults. There is no serological marker nor laboratory estimation available to delineate the definite presence or absence of the illness in children.

It is important to be clear that there is a difference between an ongoing aetiology such as persistent infection and an onset prompted by infection, but not maintained by ongoing infection. Whatever establishes the onset of the illness, and it appears to be a fairly abrupt onset in most patients,²⁷ it has been suggested that an interplay of social, psychological, and physical factors maintains and perpetuates it. In one study of a girls school struck by a large epidemic, 43 of 103 girls were affected.¹⁵ A viral precipitant was apparent in some, but not all. These workers felt that psychological and social factors were at work. Some clues about the nature of these factors are to be found in epidemiological research. It is prudent to examine some of these maintaining factors in the context of the epidemiological research.

Full chronic fatigue syndrome is said to affect about 1% of adults.⁵⁸ An American community study in children suggests an equal sex distribution, with a prevalence of approximately 2%.⁵⁹ A total of 561 of 914 children in a community answered a questionnaire, followed by history taking and examination, and 21 children were found to have chronic fatigue syndrome. An Australian prevalence study in a rural area found lower rates.²¹ The mean age of onset reported from different samples varies between 11 and 15 years,^{27 29 34 59} with a wide range. The sex distribution varies between published reports. More women than men are affected in adult populations.² In groups of children diagnosed with chronic fatigue syndrome in specialist clinics, the sex ratio usually favours girls and ranges from 6:4²⁸ to 4:1,³² with other studies reporting ratios between these,^{27 29 34} although community studies have found an equal sex distribution.⁵⁹ One study suggested that there was a bias in favour of higher socioeconomic groups,³⁰ but this was a specialist referral centre and the overall evidence has not confirmed this.¹⁹

Regardless of the lack of a specific single viral aetiology, it is well known that acute infections can precipitate the illness,¹ and an acute illness appears to precede the fatigue in about two thirds of children seen in paediatric outpatient departments.^{29 34} Responses to convalescence and rehabilitation are varied and may be important in the development of the illness.⁶¹ In children, such issues are influenced by family factors. These include over protectiveness,³³ over involvement,⁶² a powerful commitment by parents either to the notion of the illness (for example, "ME") as an untreatable physical disorder,⁶³ or to a self help group that rejects rehabilitative interventions.³³ Some workers have suggested that in a small minority of affected children the syndrome reveals more about the emotional needs of the parents than the child, and that a variant of Munchausen by proxy may be "ME by proxy".⁶⁴

Some patients have other family members with chronic fatigue syndrome^{34 59} or other chronic illnesses.⁶² In a cluster of 32 patients in Buffalo (USA), the adult family members of 50% of the children were also affected.³⁷ Clusters may be related to infection or the modelling of responses to illness within the family or in communities,¹⁵ and systemic dynamics must always be considered. Some workers have drawn parallels⁶⁵ with Taylor's understanding of conversion disorders.⁶⁶ He suggests that a child may find himself or herself in a predicament that needs an illness to resolve it and an ally (such as a parent) who helps to perpetuate the illness. For example, Waller and Eisenberg⁶⁷ described "the masquerade syndrome" where school refusal was disguised as a physical illness, and where powerful protective instincts in the parents maintained an absence from school. School non-attendance is common in chronic fatigue syndrome,^{28 29 30 32 62 68} with children who attend a clinic often having had at least one full term off school and some having considerably more.³⁰

In one sample of a paediatric infectious diseases clinic in the USA, 44% of children had a home tutor.²⁹ In the Buffalo cohort nearly 38% of affected children missed more than six months of school.³⁷ An editorial in the *British Medical Journal* makes the point that many children with other serious illnesses including malignancies, cystic fibrosis, and rheumatological disorders may have surprisingly little time away from school in comparison.⁶⁹ Some workers have suggested that chronic fatigue syndrome is the most common current cause of long term school non-attendance,⁷⁰ although this was a questionnaire based study with a relatively low number (37%) of respondents and should therefore be treated with caution.

Further work needs to be carried out into this apparent area of discrepancy between chronic fatigue syndrome and other chronic illnesses. It is important to try and understand a child's attitudes to school, especially when problems are denied.³⁰ Some workers report adolescents with high standards and an emphasis on achievement,⁶⁵ or highly successful adolescents unable to sustain early excellence,⁷¹ although many children may not fall into these

categories. There may be anxieties, learning difficulties, teasing, or bullying. Furthermore, the symptoms of the illness (such as poor concentration) may have an impact on integrating or reintegrating.³⁰

Psychiatric symptoms can coexist with chronic fatigue in adolescents,^{27 30 72} particularly depression,^{27 31} although many children and adolescents have no significant problems in this area. Depression is associated with chronic fatigue syndrome in 60–80% of children.⁷³ Many people with fatigue have psychiatric symptoms and illnesses, and the relation with the fatigue and its associated problems is not always straightforward or easy to clarify. Those with depression are more likely to have somatic symptoms⁴⁰ and somatisation is a feature that is reported in association with chronic fatigue syndrome in children,^{28 65 74} although this is hardly surprising given the defining characteristics of chronic fatigue syndrome. In a case-control study children with chronic fatigue syndrome showed significantly increased psychological distress, with internalisation, withdrawal, and socialisation difficulties²⁸ compared with healthy controls. Fifteen adolescents with the symptoms of chronic fatigue syndrome and with normal results of investigations were found to have higher levels of depressive symptoms than adolescents in a medical clinic, but lower levels than depressed controls.⁷⁵ Some workers have tried to discriminate between depressed subjects and those with chronic fatigue syndrome,²⁷ although it has also been argued that attempting to discriminate is artificial as the illness has physical and psychological components. Some items have been purported to discriminate.²⁷ The two best discriminators reported were a past history of seeing a child psychiatrist being more likely in depression, and sudden (rather than gradual) fatigue symptom onset being more likely in chronic fatigue syndrome without depression. Carter *et al* have suggested that a multicentre trial should be set up to develop an inventory to identify children with clear evidence of depression and those with chronic fatigue with no depression.²⁷ Significant life events may be relevant. Prominent examples would be loss and bereavement, which have been reported in conjunction with chronic fatigue syndrome.^{62 76}

Some children and their families become locked into a belief system that encourages excessive rest, adoption of the sick role, and withdrawal from social activity and school. In the past, total and prolonged rest was recommended.³ We suggest that this is damaging because of the profound physiological consequences explained earlier. Nevertheless, many clinicians appear to continue recommending long term rest. Rest and withdrawal promote muscle wasting, joint stiffness, and increasing fatigue, with subsequent exercise induced exhaustion leading to a misplaced confirmation of serious illness. Excessive rest may occasionally lead to contractures.¹¹ Several workers have expressed their concern about clinical advice that advocates “complete” bed rest.^{77 78} All of these issues, together with asso-

ciated dependence and despondency, help to perpetuate the illness. The resultant social and educational estrangement makes reintegration to school at best difficult, and at worst almost impossible. A model of “learned helplessness” based around a belief in an external causal agent and an ensuing self perpetuating and disempowering cycle has therefore been proposed⁶⁶ and is used as a basis for treatment by many clinicians.

Management

Many physical illnesses may have fatigue as a symptom. It is clearly important to exclude common causes of prolonged fatigue such as anaemia and hypothyroidism, and a good history and examination may point the way to other potential causes such as arthritis,⁷⁴ inflammatory bowel disease,²⁹ and diabetes mellitus.²⁸ Numerous tests have been suggested for a patient presenting with prolonged fatigue.³⁵ Referrals to a specialist infectious diseases clinic (where we might expect to have a high percentage of organic findings) have not, however, found batteries of tests to be particularly helpful.^{28 34}

As with adults,³² most doctors working with such children are keen to announce the merits of professionals cooperating.⁶⁹ In children, this means child health teams working together with child mental health teams.^{33 76} Several workers have recommended that a holistic approach to the problem should be taken, with attention being paid to emotional, social, and family factors.⁷³ This requires all aspects of treatment, including family and school factors, to be considered in the rehabilitative process.

To engage the child and family, and to gain an understanding of their predicament, it is important to acknowledge the reality of the child's symptoms and to listen carefully to their beliefs and attributions about the illness.³⁴ As with all illnesses, the clinician and the family need to find a common explanation that considers both the physical and psychological aspects of the illness, and which can then be used as a basis for understanding and planning interventions.⁶² In chronic fatigue syndrome this may mean a shift away from an exclusively physical understanding of the illness.^{34 79} We recommend a new approach, promoting a physiological understanding of the illness that incorporates the physical, psychological, and social elements of the illness without allowing the physical and psychological aspects to be split. The notion that nothing can be done, that the patient should avoid mental or physical activity and wait for either a remission or a medical cure, should be sensitively challenged with the encouragement of more optimism.⁶⁹

A clear explanation of the physiological basis of the illness is crucial. This can be achieved using a flow chart and systematically going through the development of the illness affecting the child with the clinician. It will be important to explain the vicious cycles involved with muscle wasting, rest, exercise induced exhaustion, and more rest leading to more wasting. Other similar vicious cycles (involving eating habits, sleeping habits, and so on)

should all be carefully explained. The importance of this psychoeducational process as a way of engaging the family in a common understanding of the illness should not be underestimated. Rapport and the therapeutic alliance between family, child, and clinician is a central ingredient.

A graded and gradual increase in exercise (gentle, if necessary) and rehabilitation is now encouraged by most experienced clinicians^{19 32 33-35 78 80 81} and a randomised controlled trial in adults showed it to be more useful than flexibility exercises and relaxation therapy.⁸²

Useful techniques include cognitive behavioural approaches,³⁵ which concentrate on shifting the belief system about the illness from one relying on exercise avoidance and a negative stance, to one that acknowledges the importance of a positive attitude to rehabilitation with a physiological understanding of the illness at its centre, and with the family engaged on that pragmatic, common sense basis. Behavioural approaches aimed at increasing activity³² may be used. Operant conditioning with rewards may be used in an adjunctive way.³³ As with adult studies, the intention is to explore and renegotiate beliefs that have resulted in detrimental coping behaviours, switching instead to more adaptive, helpful beliefs and coping strategies.^{76 83-85} The process is most effective when the re-evaluation of the illness beliefs is carried out in close collaboration with the patient and their family.^{62 80 86} These approaches can be developed within a family context⁸⁰ with consideration of transgenerational issues.⁶² The importance of this process of collaboration has been reaffirmed in published work with adults.⁸⁵ Lask and Dillon have made the point that often the children who do not improve are those with parents who are unwilling or unable to accept or cooperate with treatment.¹¹

Where school absence and social isolation have arisen, graded reintegration with peer and school activities is recommended,¹⁹ with a return to school as early as possible.³⁴ Home tuition may interfere with a return to school and all the attendant benefits that arise from being back at school,² but some workers endorse it in some circumstances.⁶⁹ Short periods of time at school are preferable to none at all.

The use of drugs has not been explored well in children. In adult studies few advantages have been found.⁸³ Despite the frequent presence of depression in adults, antidepressants often appear to have little or no effect^{31 32} and, given poorer response rates to antidepressants in children, are not likely to be helpful in all but exceptional circumstances. High dose acyclovir has been shown to be ineffective in a controlled adult study.⁸⁷ Findings from the use of high dose intravenous immunoglobulin have been conflicting, not always convincing, and in any case involve relatively high rates of adverse effects.^{88 89}

Outcome

Reported outcomes vary.^{2 34} This is likely to be related to the fact that different groups are studied, treatment approaches differ, and there are different attrition rates. Some children are lost to follow up because of resistance from the children themselves or their families, and this may be as high as 40%.³² This may in part be related to the family or child's belief that the illness is exclusively physical³¹ and requires no involvement from a child mental health team, a notion that is encouraged by some self help groups. Several years ago one ME support group produced a fact sheet for children that recommended that if general practitioners attempted a referral to a child psychiatrist or suggested graded exercise, the family should change their doctor immediately.³⁵

Thankfully, this situation has moved on, with many clinicians recognising the disorder and with self help groups now working with professionals to seek good provision of services. Action for ME and Chronic Fatigue is a support group whose current publications on children recommend that total bed rest should be avoided unless the child is acutely ill, and that graded rehabilitation has a place if not used over zealously, and this is a more comfortable stance for professionals to work with.⁹⁰

The Action for ME and Chronic Fatigue publications on children make the statement that "the average illness in teenagers lasts about four and a half years".⁹⁰ The reference it uses for this⁹¹ is a paper reporting a specialist clinic taking referrals for microbiological diagnosis. From the 6000 referred patients (age range 7-64 years), only 34 children under the age of 16 years were diagnosed as having "ME" and there is no breakdown of the duration of illness by age. It is therefore a small number of children, it is not an epidemiological or community based study, and it is difficult to see how this paper can be quoted to give prognostic information about children with chronic fatigue syndrome. In any case, the figure quoted contradicts other research looking at children.

It is true that the minority of children who need to be admitted to a paediatric ward may have a less favourable prognosis. In one series approximately 30% of this group were shown to have symptoms resistant to treatment that persisted for years.⁹² However, most children have a better prognosis. One sample of paediatric outpatients had a good overall outcome in nearly 95% of cases.³⁴ This was after a programme of treatment involving an early return to school, a gradual increase in exercise, and careful attention to maintaining factors. Another specialist clinic has reported half the children being well or noticeably improved after "one to two years".³¹ In an outpatient study of children referred with at least four months of fatigue, 77% had either returned to normal or improved with occasional "relapses" after a median of 17 months.²⁸ Follow up of 23 children diagnosed as having chronic fatigue syndrome in another clinic found that most children had recovered after a

median follow up of two years.²⁹ This infectious diseases sample found that 76% reported a definite improvement at two years, with 38% continuing to have some occasional residual symptoms.²⁹ One girl from 23 children was still bedridden two years after referral,²⁹ and she had several family members with a similar illness.

Persistent long term fatigue is less common than the media suggests. In general, over three quarters of children at the more severe end of the spectrum (requiring referral to specialist clinics) should expect to be back to normal or considerably improved by two years, and other studies with comprehensive treatment approaches do much better than this.³⁴

Further work

Research in this area is important clinically because of the profound social, educational, and developmental effects that chronic fatigue syndrome can have in children and young people. Chronic fatigue syndrome also carries significant resource implications for both the community and the health service.⁹³ Studies reporting follow up from community samples would be helpful to clarify the natural history and range of possible outcomes.

We found no study where rest has been researched as an ongoing strategy for dealing with childhood chronic fatigue syndrome, despite some clinicians recommending its use in some patients,⁹¹ and a widespread belief in the community that it plays a key role in the management of the illness. Many clinicians have aligned themselves with the view that prolonged rest is harmful, but only a well planned randomised study comparing different periods of rest before embarking on graded rehabilitation will resolve the polarisation between clinical services and some sufferers and support groups. Such polarisation is in itself unhelpful and sometimes harmful. Most clinicians and self help groups, as well as families, genuinely want the best for the children, but for treatment to be successful they need to work together. Any collaborative project or development that can achieve this will be for the benefit of patients with chronic fatigue syndrome.

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- 1 Straus SE. Chronic fatigue syndrome. *BMJ* 1996;**313**:831–2.
- 2 Report of the Working Party of the Royal Colleges of Physicians, Psychiatrists and General Practitioners. *Chronic fatigue syndrome: Cr54*. London: RCP, 1996.
- 3 Beard GM. Neurasthenia or nervous exhaustion: *Boston Medical and Surgical Journal* 1869;**80**:213–21.
- 4 McKenzie R, Straus SE. Chronic fatigue syndrome. *Adv Intern Med* 1995;**40**:119–53.
- 5 Bell DS, Bell KM, Cheney PR. Primary juvenile fibromyalgic syndrome and chronic fatigue syndrome in adolescents. *Clin Infect Dis* 1994;**18**(suppl 1):S21–3.
- 6 Wessely S. Old wine in new bottles: neurasthenia and “ME”. *Psychol Med* 1990;**20**:35–53.
- 7 Henderson DA, Shelokov A. Epidemic neuromyasthenia—clinical syndrome? *N Engl J Med* 1959;**260**:757–64.
- 8 Richardson AT. Some aspects of a Royal Free Hospital epidemic. *Ann Phys Med* 1956;**3**:81–9.
- 9 Behan PO, Behan WMH, Bell EJ. The postviral fatigue syndrome: an analysis of the findings in 50 cases. *J Infect* 1985;**10**:211–2.
- 10 Byrne E. Idiopathic chronic fatigue and myalgia syndrome (myalgic encephalomyelitis): some thoughts on nomenclature and aetiology. *Med J Aust* 1988;**148**:18–82.
- 11 Lask B, Dillon MJ. Post-viral fatigue syndrome [editorial]. *Arch Dis Child* 1990;**65**:1198.
- 12 Yunus MB. Fibromyalgia syndrome: new research on an old malady. *BMJ* 1989;**298**:474–5.
- 13 Garraza ME. Somatisation in children. *J Child Psychiatry Psychol* 1996;**37**:13–33.
- 14 Isaacs R. Chronic infectious mononucleosis. *Blood* 1948;**3**:858–61.
- 15 Mary PGR, Dounan SPB, Ashton JR, et al. Personality and medical perception in benign myalgic encephalomyelitis. *Lancet* 1980;**iii**:1122–4.
- 16 Galpine JF, Brady C. Benign myalgic encephalomyelitis. *Lancet* 1957;**ii**:757–8.
- 17 Hall DG, Sanders SD, Replogle WH. Fatigue: a new approach to an old problem. *J Miss State Med Assoc* 1994;**35**:155–60.
- 18 Holmes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome: a working case definition. *Ann Intern Med* 1988;**108**:387–9.
- 19 Dale JK, Straus SE. The chronic fatigue syndrome: considerations relevant to children and adolescents. *Adv Pediatr Infect Dis* 1992;**7**:63–83.
- 20 Lloyd AR, Wakefield D, Boughton C, Dwyer J. What is myalgic encephalomyelitis? *Lancet* 1988;**ii**:1286–7.
- 21 Lloyd AR, Hickie I, Boughton CR, et al. Prevalence of chronic fatigue syndrome in an Australian population. *Med J Aust* 1990;**153**:522–8.
- 22 Sharpe M, Archard L, Banatvala J, et al. Chronic fatigue syndrome: guidelines for research. *J R Soc Med* 1991;**84**:118–21.
- 23 David A, Wessely S, Pelosi A. Myalgic encephalomyelitis or what? *Lancet* 1988;**ii**:100–1.
- 24 Manu P, Lane TJ, Matthews DA. The frequency of the chronic fatigue syndrome in patients with symptoms of persistent fatigue. *Ann Intern Med* 1988;**109**:554–6.
- 25 Straus SE. Defining the chronic fatigue syndrome. *Ann Intern Med* 1992;**116**:1569–70.
- 26 Fukuda K, Straus SE, Hickie I, et al. Chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Intern Med* 1994;**121**:953–9.
- 27 Carter BD, Kronenberger WG, Edwards JF, et al. Differential diagnosis of chronic fatigue in children: behavioural and emotional dimensions. *Developmental and Behavioural Pediatrics* 1996;**17**:16–21.
- 28 Carter BD, Edwards JF, Kronenberger WG, et al. Case control study of chronic fatigue in pediatric patients. *Pediatrics* 1995;**95**:179–86.
- 29 Marshall GS, Gesser RM, Yamanishi K, Starr SE. Chronic fatigue in children: clinical features, Epstein–Barr virus and human herpes virus 6 serology and long term follow up. *Pediatr Infect Dis J* 1991;**10**:287–90.
- 30 Walford GA, Nelson WM, McCluskey DR. Fatigue, depression and social adjustment in chronic fatigue syndrome. *Arch Dis Child* 1993;**68**:384–8.
- 31 Smith MS, Mitchell J, Corey L, et al. Chronic fatigue in adolescents. *Pediatrics* 1993;**88**:195–202.
- 32 Vereker MI. Chronic fatigue syndrome: a joint paediatric–psychiatric approach. *Arch Dis Child* 1992;**67**:550–5.
- 33 Rikard-Bell CJ, Waters BGH. Psychosocial management of chronic fatigue syndrome in adolescence. *Aust N Z J Psychiatry* 1992;**26**:64–72.
- 34 Feder H, Dworkin P, Orkin C. Outcome of 48 pediatric patients with chronic fatigue: a clinical experience. *Archives of Family Medicine* 1994;**3**:1049–55.
- 35 Wessely S. Chronic fatigue syndrome—the current position: 2. Assessment and treatment. *Primary Care Psychiatry* 1995;**1**:87–98.
- 36 Wessely S. Chronic fatigue syndrome—the current position: 1. Background, epidemiology and aetiology. *Primary Care Psychiatry* 1995;**1**:21–30.
- 37 Levine PH, Krueger GRF, Straus SE. The postviral chronic fatigue syndrome: a round table. *J Infect Dis* 1989;**160**:722–4.
- 38 Gow J, Behan P, Simpson K, et al. Studies of enteroviruses in patients with chronic fatigue syndrome. *Clin Infect Dis* 1994;**18**(suppl 1):S126–9.
- 39 Mawle A, Nisenbaum R, Dobbins J, et al. Seroepidemiology of chronic fatigue syndrome: a case control study. *Clin Infect Dis* 1995;**21**:1386–9.
- 40 Thomas PK. The chronic fatigue syndrome: what do we know? That it's a complex interaction of cerebral dysfunction, trigger factors, and social attitudes. *BMJ* 1993;**306**:1557–8.
- 41 Demitrack MA, Dale JK, Straus SE, et al. Evidence for impaired activation of hypothalamic–pituitary–adrenal axis in patients with chronic fatigue syndrome. *J Clin Endocrinol Metab* 1991;**73**:1224–34.
- 42 Bakheit AMO, Behan PO, Dinan TG, et al. Possible up-regulation of hypothalamic five hydroxy-tryptamine receptors in patients with postviral fatigue syndrome. *BMJ* 1992;**304**:1010–2.
- 43 Dunstan RH, Donohoe M, Taylor W, et al. A preliminary investigation of chlorinated hydrocarbons and chronic fatigue syndrome. *Med J Aust* 1995;**163**:294–7.
- 44 Landay AL, Jessop C, Lennette ET, Levy JA. Chronic fatigue syndrome: clinical condition associated with immune activation. *Lancet* 1991;**338**:707–12.
- 45 Straus SE, Dale JK, Peter JB, Dianarello CA. Circulating lymphokine levels in chronic fatigue syndrome. *J Infect Dis* 1989;**160**:1085–6.
- 46 Klimas NG, Salvato FR, Morgan R, Fletcher MA. Immunologic abnormalities in chronic fatigue syndrome. *J Clin Microbiol* 1990;**28**:1403–10.

- 47 Subira ML, Castilla A, Civeira M, Prieto J. Deficient display of CD3 on lymphocytes of patients with chronic fatigue syndrome. *J Infect Dis* 1989;160:165–6.
- 48 Costa DC, Brostoff J, Douli V, Ell PJ. Brain stem hypoperfusion in patients with myalgic encephalomyelitis—chronic fatigue syndrome. *Eur J Nucl Med* 1992;19:733.
- 49 Greenleaf JE. Physiological responses to prolonged bed rest and fluid emersion in humans. *J Appl Physiol* 1984;57:619–33.
- 50 Ferrando AA, Stuart CA, Brunder DG, Hillman GR. Magnetic resonance imaging quantitation of changes in muscle volume during seven days of strict bed rest. *Aviat Space Environ Med* 1995;66:976–81.
- 51 Bloomfield SA. Changes in musculoskeletal structure and function with prolonged bed rest. *Med Sci Sports Exerc* 1995;29:197–206.
- 52 Appell HJ. Muscular atrophy following immobilisation. A review. *Sports Med* 1990;10:42–58.
- 53 Booth FW, Lou W, Hamilton MT, Yan Z. Cytochrome c mRNA in skeletal muscles of immobilised limbs. *J Appl Physiol* 1996;81:1941–5.
- 54 Sargeant AJ, Davies CT, Edwards RH, et al. Functional and structural changes after disuse of human muscle. *Clin Sci Molec Med* 1977;52:337–42.
- 55 Duchateau J. Bed rest induces neural and contractile adaptations in triceps surae. *Med Sci Sports Exerc* 1995;27:1581–9.
- 56 Schmitt DA, Schaffar L, Taylor GR, et al. Use of bed rest and head down tilt to stimulate spaceflight induce immune system changes. *J Interferon Cytokine Res* 1996;16:151–7.
- 57 Haruna Y, Suzuki Y, Kawakubo K, et al. Decremental reset in basal metabolism during 20 days rest. *Acta Physiol Scand Suppl* 1994;616:43–9.
- 58 Pawlikowska T, Chalder T, Hirsch SR, et al. Population based study of fatigue and psychosocial distress. *BMJ* 1994;308:763–6.
- 59 Bell KM, Cookfair D, Dell DS, et al. Risk factors associated with chronic fatigue syndrome in a cluster of pediatric cases. *Rev Infect Dis* 1991;13:32–8.
- 60 Withdrawn
- 61 Imboden J, Carter A, Cluff L. Convalescence from influenza: a study of the psychological and clinical determinants. *Ann Intern Med* 1961;108:393–9.
- 62 Pipe R, Wait M. Family therapy in the treatment of chronic fatigue syndrome in adolescence. *ACPP Rev News* 1995;7:9–16.
- 63 Harris F, Taitz LS. Damaging diagnoses of ME in children [letter]. *BMJ* 1989;299:790.
- 64 Garraalda ME. Severe chronic fatigue syndrome in childhood: a discussion of psychopathological mechanisms. *Eur J Child Adolesc Psychiatry* 1992;1:111–8.
- 65 MacDonald TM. Myalgic encephalomyelitis by proxy. *BMJ* 1989;299:1030.
- 66 Butler S, Chalder T, Ron M, Wessely S. Cognitive behaviour therapy in chronic fatigue syndrome. *J Neurol Neurosurg Psychiatry* 1991;54:153–8.
- 67 Waller D, Eisenberg L. School refusal in childhood: a psychiatric/paediatric perspective. In: Herso L, Berg I, eds. *Out of school: modern perspectives in school refusal and truancy*. Chichester: Wiley, 1980:209–9.
- 68 Jones JF, Ray CG, Minnich LL, et al. Evidence for active Epstein-Barr virus infection in patients with persistent, unexplained illnesses: elevated anti-early antigen antibodies. *Ann Intern Med* 1985;102:1–7.
- 69 Marcovitch H. Managing chronic fatigue syndrome in children. *BMJ* 1997;314:1635–6.
- 70 Dowsett EG, Colby J. Long term sickness absence due to ME/chronic fatigue syndrome in UK schools: an epidemiological study with medical and educational implications. *Journal of Chronic Fatigue Syndrome* 1997;3:29–42.
- 71 Lidstone JE, Amundsen ML, Amundsen LH. Depression and chronic fatigue in the high school student and athlete. *Primary Care* 1991;18:283–96.
- 72 Strickland MC. Depression, chronic fatigue syndrome, and the adolescent. *Primary Care* 1991;18:259–70.
- 73 Bell D. Chronic fatigue syndrome in children. *Journal of Chronic Fatigue Syndrome* 1995;1:9–33.
- 74 Baetz-Greenwalt B, Jensen VK, Lee AL, et al. Chronic fatigue syndrome in children and adolescents; a somatoform disorder often complicated by treatable organic disease. *Clin Infect Dis* 1993;17:571.
- 75 Smith MS, Mitchell J, Corey L, et al. Chronic fatigue in adolescents. *Pediatrics* 1991;88:195–202.
- 76 Arav-Boger R, Spierer Z. Chronic fatigue syndrome: pediatric aspects. *Isr J Med Sci* 1995;31:330–4.
- 77 Wessely S, David A, Butler S, Chalder T. The management of chronic (post-viral) fatigue syndrome. *J R Coll Gen Pract* 1989;39:26–9.
- 78 Sidebotham P, Skeldon I, Chambers T, et al. Refractory chronic fatigue syndrome in adolescence. *Br J Hosp Med* 1994;51:110–12.
- 79 Leslie SA. Diagnosis and treatment of hysterical conversion reactions. *Arch Dis Child* 1988;63:506–11.
- 80 Wachsmuth JR, MacMillan HL. Effective treatment for an adolescent with chronic fatigue syndrome. *Clin Pediatr* 1991;30:488–90.
- 81 Cox D, Findley L. Chronic fatigue syndrome in adolescence [letter]. *Br J Hosp Med* 1994;51:614.
- 82 Fulcher KY, White PD. Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. *BMJ* 1997;314:1647–53.
- 83 Wilson A, Hickie I, Lloyd A, Wakefield D. The treatment of chronic fatigue syndrome: science and speculation. *Am J Med* 1994;96:544–50.
- 84 Surawy C, Hackmann A, Hawton K, Sharpe M. Chronic fatigue syndrome: a cognitive approach. *Behav Res Ther* 1995;33:535–44.
- 85 Sharpe M, Hawton K, Simkin S, et al. Cognitive behaviour therapy for the chronic fatigue syndrome: a randomised controlled trial. *BMJ* 1996;312:22–6.
- 86 Graham H. Family interventions in general practice: a case of chronic fatigue. *J Fam Ther* 1990;13:225–30.
- 87 Straus SE, Dale JK, Tobi M, et al. Acyclovir treatment of the chronic fatigue syndrome. Lack of efficacy in a placebo controlled trial. *N Engl J Med* 1988;319:1692–7.
- 88 Peterson PK, Shepard J, Macres M, et al. A controlled trial of intravenous immunoglobulin G in chronic fatigue syndrome. *Am J Med* 1990;89:554–60.
- 89 Lloyd A, Hickie I, Wakefield D, et al. A double blind, placebo controlled trial of intravenous immunoglobulin therapy in patients with chronic fatigue syndrome. *Am J Med* 1990;89:561–8.
- 90 Franklin A. Children with M.E. Guidelines for school doctors and nurses and general practitioners. *Action for ME and Chronic Fatigue Newsletter* 1997:1–10.
- 91 Dowsett EG, Ramsay AM, McCartney RA, Bell EJ. Myalgic encephalomyelitis—a persistent enteroviral infection. *Postgrad Med J* 1990;66:526–30.
- 92 Roberts H, Clayden G, Milavic G. A long term follow-up study of children and adolescents with chronic fatigue syndrome (ME). Annual Residential Conference of the Child and Adolescent Section of the Royal College of Psychiatrists, Swansea, 1992.
- 93 Lloyd AR, Pender H. The economic impact of chronic fatigue syndrome. *Med J Aust* 1992;157:599–601.