
Chronic Fatigue Syndrome
Report of a joint working group of the Royal Colleges of Physicians,
Psychiatrists, and General Practitioners

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Preface

Disabling severe chronic exhaustion and the choice of diagnostic labels or categories used to describe the syndrome and associated symptoms are issues of great public concern and debate.

There are differing and strongly held views on the cause of chronic fatigue syndrome, on its relationship to other disease categories, on the best approach to relief of symptoms, on the longterm outlook and on the appropriate role of health professionals. Attitudes to those who are afflicted and their families also vary. Curiously there is less interest in prevention.

This report has been prepared at the request of the Chief Medical Officer and has been written by a working party on behalf of the Royal Colleges of Physicians, Psychiatrists and General Practitioners. It aims to provide a basis of informed, multidisciplinary medical opinion from which the issues surrounding chronic fatigue syndrome (CFS) can be viewed.

The authors have extensive clinical experience in CFS and associated syndromes. However, they have not based the report solely on that experience but have also drawn from the available methodologically sound research literature. Where this evidence leads to clear conclusions they indicate them. Where there is continuing uncertainty, they say so.

The report is timely for two reasons. First, a number of recent publications have shed important light on this topic but some of them are not yet well known outside the research community. Second, it is the aim and policy of both the medical professions and of government that health and medical care in Britain should become increasingly 'knowledge based'. The need for such an approach, in which diagnosis and treatment are based on sound research evidence, should apply equally to the difficult problems posed by CFS as to other areas of health care.

In compiling this report the committee have drawn extensively on the work of others. In particular, we and the authors wish to draw attention to the recent report on CFS coordinated by the charity Westcare. Whilst we are not in agreement with all the findings of that report, we acknowledge our debt to Dr David Tyrrell and his colleagues. We hope that this report builds up on their work.

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CHAPTER 1

Terms of reference

1.1 The Chief Medical Officer of the Department of Health has requested a report from the Academy of Medical Royal Colleges (formerly Conference of Colleges) concerning chronic fatigue syndrome (CFS), to advise on matters such as diagnosis, clinical practice, aetiology and service provision. The residents of the Royal Colleges of Physicians, Psychiatrists and General Practitioners have nominated an expert committee to carry out this task (Appendix 1). All the members of the joint committee have direct clinical experience in the management of either adults or children with CFS, and most have also contributed to the peer reviewed research literature on the subject. The committee was also assisted by a Health Commissioner.

1.2 The following document is not an extensive review of CFS.1,2 Our aim is to briefly review the current state of knowledge in this area, basing our conclusions principally on published evidence but supplemented by our clinical experiences. We do not address important medico-legal issues, such as disability and insurance benefits, which are outside our terms of reference.

CHAPTER 2

Background

2.1 Patients presenting with physical symptoms for which it is not possible to give a clear medical explanation are not new. Such symptoms might include unexplained chest pain, dizziness, headache, back pain, joint and muscle pains, bowel and bladder dysfunction, throat discomfort, and chronic fatigue. Patients are often troubled by several of these symptoms.³⁻⁶ The Royal Colleges of Physicians and Psychiatrists have already collaborated on projects concerning the psychological care of medical patients.^{7,8} Some of the main points which emerge from their reports and related publications on unexplained symptoms and associated problems⁹ are:

- These symptoms and problems are common in general practice and are also encountered in most specialist clinics.
- They have a wide range of severity, from the relatively minor to serious suffering and disability.
- They show a consistent association with emotional morbidity, especially symptoms of depression and anxiety.
- These problems are often poorly managed by doctors - there is a tendency to over-investigate using laboratory and imaging techniques and not to explore mental state abnormalities. Some patients gain the impression that they are being told there is 'nothing wrong' when all investigations are negative.
- Aetiology and classification of these symptoms and syndromes is controversial. The Royal Colleges have stressed that approaches to these patients should not be based on simple biomedical models. Rather, they advocate a combined biological, psychological and social approach in formulating what predisposes to, what precipitates and what perpetuates the symptoms. This will be addressed in greater detail later in this report.
- Specific psychological skills may be required in treating some patients. For those with severe emotional morbidity, psychological or psychiatric input should be available.
- These overlapping symptoms and syndromes are major public health problems which should receive more attention in orthodox medical practice with increased service provision and research.

2.2 Why has it been necessary for the Chief Medical Officer to ask the Royal Colleges to produce a report specifically on syndromes of chronic fatigue ? One reason is to review and update a recent report produced by a National Task Force, an initiative of the charity Westcare.¹⁰ Why, however, was that report considered necessary ? We believe that a combination of factors has contributed to particular difficulties in diagnosis and management of chronic fatigue. These are discussed below.

2.3 Fatigue is one of the most common complaints encountered in community health surveys.¹¹ It is a feature of a wide range of both well- and ill-defined illnesses, and is also common as an isolated symptom.

2.4 Although widely discussed earlier this century, chronic fatigue lost its prominence in the medical literature sometime after the First World War.¹²⁻¹⁴ For many years fatigue syndromes were not a major issue for doctors or the professional and lay journals. This began to alter in the 1980s for a variety of reasons. Amongst those were a series of widely publicised claims on both sides of the Atlantic for a viral aetiology of otherwise unexplained fatigue. Although some of these claims were in

retrospect premature (see Chapter 4) they attracted considerable interest from patients, doctors and the media, and were probably instrumental in the formation of active self help and pressure groups.

2.5 The revival of interest in chronic fatigue and related syndromes has had many beneficial effects. For example, media attention has successfully highlighted shortcomings in service provision for such patients (see Chapter 12) and may have influenced research funding in this area. Other consequences, visible not only in the popular but also the medical literature, have been less welcome. Legitimate medical controversies have been misinterpreted. Important and necessary nosological debates have been misrepresented. Proper consideration of the importance of psychosocial issues in fatigued patients has been framed as a contrast between 'real' disease and 'mere' psychiatric illness which is erroneously viewed as self-induced.

2.6 Controversy has been heightened by the recent prominence of the diagnostic label 'myalgic encephalomyelitis' (ME) in the United Kingdom. This was originally used to refer to epidemic outbreaks of unexplained neurological symptoms and signs¹⁵ but came to be applied to sporadic cases of severe and prolonged fatigue. Widely publicised claims arising from immunological and virological research gave medical credibility to the 'new' syndrome, but with further knowledge it became inevitable that the label of 'ME' could not be accepted by mainstream medical opinion. The precise reasons for this disillusion will be outlined later, but the result has been a difference between popular and professional opinion on the subject, which has occasionally been intense.

2.7 Widespread publicity appears to have led to over-diagnosis of ME by some doctors, allied to frequent self-diagnosis by some patients. At present we believe that the label of ME is being used inappropriately to cover a variety of diverse conditions and situations. For example, in clinical practice we have noted that the label of ME has been used by doctors and others for the following situations, emphasising an unacceptable diversity of use:

- Severe, unexplained fatigue and exhaustion.
- Unexplained syndromes of fatigue and myalgia characterised by physical symptoms without demonstrable structural pathology. Doctors, depending on their speciality or approach would refer to these various illnesses by terms such as somatoform disorder, irritable bowel syndrome, atypical facial pain, fibromyalgia, 'food allergy' syndromes, effort syndrome and many others.
- Mild, moderate or severe anxiety or depressive syndromes.
- Patients with long histories of multiple unexplained symptoms and disability who fulfil criteria for Briquet's Syndrome or somatisation disorder.
- Unexplained loss of functions such as conversion disorders.
- *Intolerable social and other stresses.
- Conditions such as ischaemic heart disease, multiple sclerosis or endocrine disorders misdiagnosed as ME.
- Over-training syndromes.
- Patients whom doctors find difficult to help.

2.8 Another reason for requesting a report from the Academy of Medical Royal Colleges is widespread uncertainty surrounding issues of treatment and prognosis. This will be addressed in Chapters 8 and 9.

CHAPTER 3

Definitions

3.1 The most appropriate term for this syndrome is chronic fatigue syndrome (CFS), which is accurate and free from unproven aetiological claims. CFS can be operationally defined, which will aid future research and clarify aspects of clinical practice. Useful parallels are the American Rheumatological Association definition of fibromyalgia¹⁷ and the working team report on functional bowel disorders.¹⁸

3.2 A number of definitions have been proposed for CFS. We support the use of defined criteria whose reliability can be tested using tried and proven methodologies. The most promising are those recently introduced by the Center for Diseases Control in Atlanta, the so-called 1994 CDC criteria,¹⁹ and those produced as a result of a consensus conference held in 1991 in this country, the so-called Oxford criteria²⁰ (see Appendix 3). We are unable to choose between these until further research establishes their validity. We do not endorse other criteria that have neither been published in the peer reviewed research literature, nor subjected to empirical scrutiny. Progress in this area will result only from the widespread use of operationally defined criteria for CFS.

3.3 It has been suggested that the term CFS is likely to lead to confusion with chronic fatigue in general and to underestimate the severity of the condition.¹⁰ It is, however, well recognised that other syndromes, eg the irritable bowel syndrome, can be graded according to severity, and that different treatment strategies are appropriate for mild, moderate and severe forms.²¹ We feel chronic fatigue syndrome should similarly be seen as covering a spectrum of severity.

3.4 Some would prefer to continue to use the term ME. It has been suggested that 'the merits of the term ME are that it emphasises the physical aspects of the condition'.¹⁰ However, encephalomyelitis describes a distinct pathological process of inflammation of the brain and spinal cord. The term ME thus erroneously endorses the existence of a specific pathological process for which in the context there is no evidence. Patients may wish to keep a particular term because only with that label are they eligible to call upon the welfare state for help. We agree with the recent Westcare Report that this is understandable but not satisfactory.¹⁰ We are unaware of any satisfactory definition of ME, and doubt whether an operational definition of ME is either possible or appropriate.

3.5 It has been suggested that there is a wide group of disorders, which fall under the term CFS, that are predominantly psychosocial, and a core called ME, which is more severe, has a characteristic pattern of fatigability and is primarily of organic origin. We do not agree. There is no evidence that mild forms of CFS are primarily psychological and severe forms are more likely to be organic in origin. Available evidence suggests the opposite - the group within CFS with more symptoms, profounder fatigability, greater disability, and longer illness duration is the subset with the strongest associations with psychological disorder.²²⁻²⁴ Such an association does not indicate that psychological disorder is the cause of greater disability. However, this does indicate that suggestions that the greater the severity of symptoms or disability, the greater the chance of finding an 'organic' aetiology are misguided.

3.6 Some definitions of CFS exclude people who have marked psychological symptoms in association with the fatigue.²⁵ This excludes approximately three quarters of people with CFS, as defined by the Oxford criteria. The division is not clinically useful, but may have relevance for specific research endeavours. The Oxford criteria do define a subgroup with fatigue symptoms occurring after an infectious disease-post-infectious fatigue syndrome-but also state that this cannot be assessed solely by retrospective recall.

3.7 The term neurasthenia has also been suggested as another term for CFS (see Glossary). In previous generations most of those who now receive the label of CFS would have been considered as neurasthenic.^{14,26} The World Health Organisation International Classification of Diseases (ICD-10) category of neurasthenia also has considerable overlap with CFS.²⁷ Of those seen in a Welsh CFS clinic, 97% also fulfilled criteria for neurasthenia.²⁸ Nevertheless, we note that this term is viewed by some as representing a narrow range of aetiologies, and is unlikely therefore to be used widely.

3.8 Reviewing the merits and meanings of the terms ME and CFS, we conclude that the term ME is a label applied to a wide variety of forms of fatigue. Relevant research on its meaning and usage will, and has, come from historical analysis, together with sociological, psychological and anthropological research (for example the development of such labels as 'Yuppie flu').

3.9 Establishing appropriate and uniform terminology is essential to the progress of clinical and scientific research in this area. We will use CFS throughout this document to refer to the range of disorders included within this term.

Summary

The term chronic fatigue syndrome (CFS) can be operationally defined for clinical and research purposes. The term CFS also allows clinicians to communicate effectively with patients and to propose a management plan while admitting that our understanding of the syndrome is incomplete. The term ME and similar terms are used to cover a wide variety of clinical and other complaints. They cannot be used for systematic research and may mislead patients into believing they have a serious and specific pathological process affecting their muscles and brain. The value of research into these syndromes will be enhanced if future studies use standardised criteria for CFS, including a measure of severity, for the purposes of comparison.

CHAPTER 4

Epidemiology

4.1 The historical literature contains many examples of outbreaks of unusual illnesses, often in confined institutions, of which the most well known was the, still controversial, episode that affected the staff of the Royal Free Hospital in 1955, and was the origin of the term myalgic encephalomyelitis.¹⁵ The aetiology and nature of the contagion in these epidemics have never been satisfactorily explained, with competing infective and psychological explanations proposed.²⁹ The passage of time means that such controversies are unlikely ever to be resolved. However, there are many important distinctions between so-called epidemic and sporadic cases of CFS. The case descriptions of epidemics are different from those of the sporadic cases that are the predominant concern. The epidemics themselves have been ill-defined, heterogenous and often poorly researched - with different case descriptions and different alleged modes of transmission.^{30,31} It is extremely unlikely that any single explanation exists uniting these phenomena, other than the shared name. It is also misleading to apply even tentative conclusions from the study of epidemics to the concern of this report - sporadic, endemic cases of chronic fatigue syndrome.

4.2 At least 25 studies exist concerning the prevalence of chronic fatigue in the community and primary care.³² Chronic fatigue as a symptom is extremely common in the community, with prevalences of between 20% and 30%.^{11,32} Most of these people neither consider themselves ill nor seek help. Chronic fatigue remains common in primary care - between 10% and 20% of attenders will admit to chronic fatigue,³³⁻³⁸ and for between 5% and 10% it will be the principal reason for consultation.^{35,39} Only a minority of these will fulfil criteria for CFS.

4.3 The epidemiology of CFS is a frequent source of confusion. Many of the current estimates of prevalence are flawed because of a failure to take into account the effect of selection bias and pathways to care. Estimates based on the experiences of clinicians in specialist centres are of little value.⁴⁰ Other studies have been based on 'key informants' such as general practitioners or hospital physicians. Factors such as attribution, recognition and recall will all seriously distort true prevalences.^{40,41} Such studies may give administrative prevalences of those with the label of ME, rather than true prevalences of CFS. The concept of 'pathways to care' is a useful one,⁴² and illustrates how studies based on population, primary, secondary or tertiary samples can each give rise to different perspectives.

4.4 These studies can also give misleading patterns of risk factors. A recent study found that from 2,398 patients with excessive fatigue only 38 (1.4%) used a label such as CFS or ME to describe their symptoms.⁴³ Only 12% of primary care cases fulfilling the complete CFS criteria used an equivalent term to refer to their illness.³⁴ Recent studies demonstrate that previous reports suggesting that teachers or health care professionals are susceptible to CFS may be influenced by selection bias and treatment seeking behaviour, and hence are not true risk factors.^{34,37,44} A similar argument applies for social class - the apparent excess of high social classes visible in all specialist clinics is probably due to selection, referral and attributional biases.^{38,44} Using selected clinic samples to answer aetiological questions inevitably leads to a failure to distinguish between risk factors for the condition, and those that reflect a tendency to seek treatment.

4.5 New epidemiological studies of improved methodological rigour have begun to emerge. Three are American in origin. In a study of an ambulatory care clinic the point prevalence of CFS varied from 0.3% to 1.0% depending on criteria.⁴⁵ In an occupational sample 0.9% fulfilled CFS criteria.⁴⁶ A study based on a Health Maintenance Organisation (HMO) in the USA reports that the point prevalence of CFS lay between 0.08% and 0.3%.⁴⁷ However, these figures need careful interpretation. Diagnoses were based on the 1988 criteria²⁵ which are now considered rather restrictive, and do not identify a distinct subgroup of patients in terms of fatigue, psychological morbidity, functional impairment or laboratory/serological measures.^{48,49} Since then the case definition has been revised, and it is no longer necessary to exclude those with common psychiatric conditions such as depression or anxiety.¹⁹ Because of the rigorous exclusions, the quoted Seattle prevalence figures are a conservative estimate of the prevalence of CFS.⁴⁷

4.6 Three British groups have now reported new epidemiological findings. A questionnaire-based study of subjects registered with a single Scottish general practice⁵⁰ reported a point prevalence of 0.6% (95% confidence intervals 0.2-1.5) according to the Oxford criteria, although based on only four cases. In a UK primary care study the point prevalence of CFS using the 1994 CDC criteria was 2.6% (95% ci 1.7-3.4%), falling to 0.5% (95% ci 0.1-0.7%) if co-morbid psychological disorders were excluded,⁵¹ similar to those obtained in another primary care study.⁵² Only 0.1% fulfilled the 1988 CDC criteria when psychiatric disorders had been excluded - similar to the American findings.

4.7 The functional impact of CFS can be profound, although this is partly tautological given that functional impairment is part of the case definition. Nevertheless, studies of chronic fatigue, CFS and post-infectious fatigue confirm that the syndromes are associated with substantial impairment in the work, social and home environments.^{36,51,53} Research has also shown that the greater the impairment,

the greater the psychological morbidity.^{49,51,54,55} Such observations do not imply causality.

4.8 CFS can be operationally defined. However, there is still no evidence that it is an independent diagnostic entity. In the current state of knowledge it remains possible, and perhaps probable, that CFS represents the arbitrarily defined end of a spectrum of symptomatic and functional impairments, which may have a number of causes. This has been suggested in the related syndrome of fibromyalgia.^{56,57} Until the nosological status of CFS is determined it may be premature to talk about precise diagnosis.

Summary

- The population point prevalence of CFS is 0.1-0.9%, using restrictive (US) criteria that exclude patients with psychiatric disorders, and 2.6% in primary care using the Oxford criteria.
- There is no clear link to social class or occupational group-such associations relate to attendance at tertiary centre clinics not prevalence in the general population.
- There are no reliable data on incidence, except after Epstein Barr virus (EBV) infection.
- Most primary care or community cases of CFS fulfil criteria for common psychological disorders; a proportion (25-40%) do not.
- Functional disability may be marked in CFS - the greater the impairment, the greater the psychological morbidity.

CHAPTER 5

Virology

5.1 There have been many claims linking viral agents with CFS over the years. One reason is the consistent observation made by patients attending specialist units that their illness began with a viral infection, and that the symptoms of persisting illness resemble those of a viral infection.

5.2 Viral agents may be associated with CFS in two distinct ways. A viral infection might be the triggering agent for CFS ('post-viral fatigue'). Alternatively, viral agents might persist in either an abnormal fashion, or an abnormal site in CFS. The latter concept that abnormal viral persistence causes CFS has received considerable attention in this country.

5.3 Establishing any link between viral infection and CFS is far from straightforward. The symptoms of viral infection are not synonymous with evidence of an infective process. There is considerable methodological complexity associated with this line of inquiry. Viral infections are common - the average person has between three and four such infections a year. Chance associations are thus hard to exclude. It is possible that infection may follow, rather than cause, fatigue ('reverse causality') - many sufferers who initially blame a virus for their illness will, on careful clinical questioning, recall a period of ill-health before the viral episode.⁵⁸ Further, depression or stress might increase the risk of a confounding viral infection⁵⁹ or of increased symptom reporting. The symptoms of infection overlap and include those of mood disorder, and may be increased by other psychological factors.⁶⁰ Post-infective syndromes have been described for many different infective agents, suggesting a non-specific association.⁶¹ There is no evidence for any single common infective agent.⁶²

5.4 There is no compelling evidence that viral persistence is uniquely associated with CFS. In this country, but not elsewhere, most attention has been devoted to enteroviruses. We note that previous reports linking various markers of enteroviral persistence, such as IgG, IgM and VP-1, with CFS are now no longer considered reliable. For example, a research group that has been strongly associated with studies linking enteroviral persistence in muscle and CFS recently failed to confirm its own findings,⁶³ and concluded that CFS was not 'dependent on persistent viral infection of muscle'. Recent case control studies have found no association between markers of enteroviral infection, including the presence of enteroviral RNA in muscle and stool samples, and CFS.^{62,64} A similar history surrounds the widely publicised claims linking the VP-1 enteroviral antigen with CFS which have not been confirmed.⁶⁵⁻⁶⁸

5.5 At present the only evidence linking enterovirus and CFS comes from a recent blinded study that detected enteroviral-specific sequences in the serum of substantially more CFS patients than both healthy controls and those with acute viral infections,⁶⁹ and that such sequences indicated the presence of distinct novel enteroviruses.⁷⁰ Such a cross-sectional association, which requires confirmation, does not allow the distinction between viral persistence as a cause of CFS, or alternatively as a consequence. At present the balance of evidence suggests that persistence of enteroviruses is unlikely to play a role in the development of CFS.⁶⁸

5.6 Researchers should be cautious about making premature causal claims, especially when reporting preliminary data which is likely to be interpreted by the media or public as 'the cause' of CFS. The recent extensive publicity that greeted a report claiming a retroviral aetiology for CFS,⁷¹ subsequently not confirmed,^{72,73} provides one such cautionary tale.

5.6 Whereas the evidence that abnormal viral persistence is of aetiological significance in CFS is weak, there is some evidence that chronic fatigue syndromes may be triggered by certain infectious episodes. These are reviewed in the next section.

5.7 The previous section (para 5.3) highlighted the many methodological difficulties in linking viral exposure and CFS. Studies of viral persistence have not been epidemiologically based. Recent research using subjects in whom viral exposure was ascertained prior to the development of CFS has shed light on the role of infective agents in precipitating, rather than causing, CFS.

These studies have been among the first to study post-infectious fatigue syndrome (PIFS), defined as a subgroup of CFS in which there is definite evidence of infection at the onset.²⁰

5.8 One study of 250 general practice patients suggests that a definable fatigue syndrome exists after glandular fever.⁷⁴ Symptoms include physical and mental fatigue (especially after exertion), excessive sleep, psychomotor slowing, poor concentration, reduced interest, social withdrawal, emotional lability, transient sore throat and painful cervical gland swelling.⁷⁵ This syndrome was found in 47% of people during the acute phase of glandular fever, compared with 20% at the onset of upper respiratory tract infections (URTI). The syndrome could be differentiated from conventional psychiatric disorders characterised by sadness and low mood. At six months, 9% still had the fatigue syndrome after glandular fever, compared with none after URTI.⁷⁶ In other words, the vast majority of sufferers of glandular fever had recovered without developing CFS, but a small minority still had the syndrome six months after onset: factors that predispose individuals to develop CFS need further elucidation.

5.9 A recent large scale primary care study of 1,199 people with clinically defined common viral infections compared to 1,167 people attending for other reasons

showed that common viral episodes were not more common in those who developed chronic fatigue or CFS.⁷⁷ Instead, the risk of both chronic fatigue and CFS was increased if there was evidence of excessive fatigue and/or psychological morbidity before acquiring an infection. This gives modern epidemiological confirmation of a classic study of recovery from influenza.⁷⁸

5.10 Another primary care study using very similar patients found that chronic fatigue after clinically defined common viral infection was associated with the patient's somatic attributional style (a person's tendency to see him or herself as suffering from a physical illness), a less definitive diagnosis of viral infection by the GP and sick certification.⁷⁹ A follow-up study of 83 cases of viral meningitis found an increased risk of CFS, although there was no difference in the risk of CFS compared to a comparison group of those with other severe non-CNS infection. The development of CFS after the infection was predicted by past psychiatric disorder and duration of time off work, but not by the severity or duration of the meningitis as reflected in number of days in hospital.⁸⁰ However, these associations may be explained by the confounding effects of concurrent psychiatric disorders or psychological distress-in other words like may predict like.

5.11 Several infectious agents may trigger chronic fatigue states.^{74,80-85} No study has reported that the infective agent itself is a maintaining factors for chronic fatigue or CFS. Instead, if a link exists between infection and chronic fatigue syndrome it might be as a general trigger promoting a behaviour pattern that in turn leads to CFS - not excluding a possible role for an immunologically mediated link between acute infection and the centrally determined behavioural response. Similar arguments have been advanced for the apparent association between infections and the development of fibromyalgia.⁸⁶

Summary

- At present there is no convincing evidence that common viral infections are a risk factor for CFS, with the exception of the fatigue syndrome that follows Epstein Barr virus (EBV). Viral infections may be only one of several possible aetiological factors in CFS, which should be regarded as being multifactorial in origin.
- Less than 10% of those with EBV infection develop CFS - the factors that distinguish these 10% from the remainder need to be explored.
- Studies in primary care have found that psychological distress, excessive fatigability and perhaps attributional style prior to clinical viral infection are risk factors for the subsequent development of CFS.

Future research needs to consider predisposing (eg personality, lifestyle or prior depression), the trigger or precipitant (eg viral illness) and maintaining factors (eg absence of a clear diagnosis, attribution, reduced exercise tolerance, societal focus on undetected infectious agent and advice to stop work).

CHAPTER 6

Muscle dysfunction and immunology

6.1 There is no consistent evidence that CFS is associated with a primary disorder of muscle, and no convincing evidence of any changes in muscle structure or function other than those secondary to inactivity.⁸⁷⁻⁹⁷ Mitochondrial abnormalities have been noted,⁹⁸ but a blinded study found no difference in the prevalence of such findings compared to normal controls.⁹⁹ As fatigue in CFS affects both physical and mental functioning and is made worse by physical and mental effort; a primary neuromuscular origin to symptoms is anyway unlikely.¹⁰⁰

6.2 The possibility that abnormalities of immune function play a role in the pathogenesis of CFS has attracted considerable attention. There have been several recent reviews of the subject,^{10,101} which draw attention to the difficulties in ascribing aetiological significance to the varied findings in view of inconsistencies. They identify the technical difficulties involved in these assays and often the nonspecific nature of observed abnormalities.

6.3 We would highlight the difficulties in interpretation of investigations (with high inter-laboratory and inter-observer variation), compounded by the failure to use similar patient groups, influenced by differences in case definition, selection and referral biases. Studies using 'subgroups' of 'chronic fatigue syndromes', defined by clinical diagnosis,¹⁰ have not produced more consistent findings.

6.4 Some use the results of immunological tests as evidence for a so-called 'organic' component in CFS, particularly when, as is usually the case, the lack of any pathognomonic symptoms, signs or laboratory abnormalities causes understandable diagnostic confusion. In this context the observed abnormalities could equally well be attributed to neuro-immunological influences, in turn related to behavioural and psychological factors in individual subjects.¹⁰¹ Such abnormalities should not deflect the clinician from the biopsychosocial approach endorsed below, and should not focus attention solely towards a search for an 'organic' cause.

6.5 We believe there is a need for further carefully controlled research in this area, with particular emphasis on possible immunological influences on the symptom complex observed in CFS patients. Until the results of such research are available, we urge against over-interpreting the abnormalities described to date.

CHAPTER 7

Psychiatry and neuropsychiatry

7.1 We agree with the statement: 'Chronic fatigue syndromes often do not fit neatly into the conventional view that disease is either physical or psychological'.¹⁰ As such, CFS does not present a new, unique problem or dilemma in medical practice.^{8,14,102} Instead CFS is another condition which highlights the difficulty that modern medicine sometimes has in responding to disorders that have both physical and psychological components, and the limitations of an overly narrow biomedical model.^{10,103,104}

7.2 Any comprehensive discussion of this subject must consider the relationship between physical and psychological factors, and between physical and psychological associations of illness.¹⁰ Much is made of the issue of 'physical' and 'psychological' symptoms and their aetiological significance in CFS. However, the presence of particular groups of symptoms is probably of little significance with regard to aetiology.¹⁰⁵ Physical symptoms can and often do arise as a result of psychological mechanisms, and vice versa. The Royal Colleges have addressed these issues in their wider context, both theoretically and practically.⁸

7.3 Over 20 studies have been published concerning the role of psychiatric disorder in CFS, of which 11 used direct interviews to diagnose psychiatric disorders.^{106,107} A variety of questionnaires, interviews and operational criteria have been used. The results are surprisingly consistent. Approximately half of those seen either in primary or specialist care with a diagnosis of one or other form of CFS fulfil criteria for affective disorder (even if the symptom of fatigue is removed from the criteria for

mood disorder). Many studies find that a further quarter fulfil criteria for other psychiatric disorders, chief amongst which are anxiety and somatisation disorders.

7.4 Before considering possible explanations for these findings we repeat Kendell's observation, made in the context of CFS: 'The statement that someone has a depressive illness is merely a statement about their symptoms. It has no causal implications'.¹⁰⁸ We also agree with Komaroff who noted that: 'One problem is that CFS is defined by a group of symptoms, without any objective abnormalities on physical examination or laboratory testing that readily establish the diagnosis. Another problem is that the same is true of depression and somatization disorder.'¹⁰⁴ So-called 'organic' factors may be equally important in those who do fulfil psychiatric criteria, and 'psychological' factors can still be important in those who do not.⁹ Social, cultural and behavioural influences may be as relevant in the minority of CFS cases who do not fulfil psychiatric criteria as in the majority who do.

7.5 There are a number of possible explanations for the repeated findings that psychological symptoms are very common in CFS:^{106,109} Reverse causality. Could the observed psychological disorder simply be a reaction to physical illness? This explanation is the least convincing. Apart from the lack of definitive evidence of a specific physical pathology, psychiatric disorders are much more common in CFS than psychological disorders in other physical illness (Table 1). Rates of operationally defined psychiatric disorder in the CFS cases are invariably in excess of those in the control subjects with better defined pathological processes.¹¹⁰⁻¹¹⁴ Selection bias of patients seen in secondary care clinics. Again, this is unlikely, because a similar proportion of patients seen in primary care with chronic fatigue syndrome also fulfil criteria for psychiatric disorder.^{37,52, 115} Differences exist, but mainly in terms of social class and explanations offered for the condition.⁴⁴ Shared origin. The possibility that both psychiatric disorder and CFS have a common neurobiological origin is appealing, not least because it draws attention to the rapidly increasing knowledge concerning the neurobiological associations of psychiatric disorder. The evidence for such links will be considered later (see paras 7.13-7.21).

Table 1: Psychiatric disorder in CFS compared to medical controls: results of five studies.

Study	Control Group	Psychiatric Disorder	Relative risk of psychiatric disorder in CFS compared to controls	
			CFS patients %	Controls %
Wessely 100	Neuro-muscular	72	36	2.0
Katon 111	Rheumatoid arthritis	45	6	7.5
Wood 110	Myopathy	41	12.5	3.3
Pepper 112	Multiple sclerosis	23	8	2.9
Johnson 113,114	Multiple sclerosis	45	16	2.8

7.6 Depression and/or anxiety represent the strongest risk factors so far identified for CFS. Any theory of the aetiology of CFS must take this observation into account. On the other hand nearly all studies find that between one-quarter to one-third of those who fulfil criteria for CFS do not fulfil any criteria for psychiatric disorder. There are also phenomenological differences between depression familiar to psychiatrists and depression in the context of CFS.^{114,116} Any simple equation of CFS with psychiatric disorder is thus erroneous.

7.7 Psychological disorders are thus one component of a multifactorial view of the aetiology of CFS. Other factors, which may be important in both the presence or absence of psychological disorder, include an as yet unidentified pathological process: altered Health perception; deconditioning; response to other factors, such as life events or sleep disturbance.

7.8 A recent study suggested that in some subjects symptoms were associated with psychiatric disorder, some with abnormal exercise responses that might result from deconditioning, and some with neither.¹¹⁷ It is thus important for researchers and clinicians to be alert to the variety of mechanisms underlying the experience of symptoms in CFS.

7.9 Patients with long histories of multiple somatic symptoms are frequently seen in CFS clinics, as they are across general medicine, where they make up 10% of new referrals.^{8,118} They may have previous episodes of unexplained abdominal pain, headaches, chest pain, food allergies, chemical sensitivities, unresolved gynaecological problems and others. Some may fulfil criteria for somatisation disorder. Most studies find that between 5% and 10% of those seen in specialist CFS clinics (but not primary care) fulfil established criteria for somatisation disorder (SD).^{48,110,111,119-121} The expected prevalence of narrowly defined somatisation disorder is of the order of 0.03-0.3%.¹²²

7.10 To a certain extent this overlap between CFS and somatisation disorder is predictable, since the definitions of both require multiple symptoms.¹²³ Patients with CFS were more likely to fulfil the criteria for somatisation disorder than chronically fatigued patients who did not fulfil the criteria for CFS.⁴⁸ These researchers concluded that the multiple symptom criteria for CFS actively select for somatisation disorder. When another group of researchers excluded those symptoms common to the definitions of CFS and SD, the prevalence of SD fell, but was still elevated above the expected levels.¹¹¹

7.11 In CFS, as with fibromyalgia, the greater the number of somatic symptoms, the greater the probability of psychiatric disorder.^{22,115} This relationship is not confined to somatisation disorder - a close relationship exists between the number of somatic symptoms and the risk of both depression and anxiety.^{41,124,125}

7.12 Patients who fulfil criteria for somatisation disorder have some of the most severe disabilities encountered in medical practice. These patients have greater functional impairment, longer illness durations and more symptoms than CFS cases without multiple symptoms.²⁴ They are probably the most difficult to treat.

7.13 Magnetic resonance imaging - Population-based studies of magnetic resonance imaging are in their infancy. At present four magnetic resonance imaging (MRI) studies of CFS have been published. Cerebral white matter abnormalities have been reported in some studies, but not all. One well conducted study found abnormalities in 27%, falling to 22% when three cases who went on to develop alternative diagnoses were excluded.¹²⁶ However, the most recent study of subjects with postviral fatigue recruited in primary care found no increase in MRI abnormalities.¹²⁷ Findings of white matter abnormalities require careful interpretation, since it is a sensitive technique and may reveal 'abnormalities' of little consequence. White matter abnormalities occur in a number of settings, and their significance remains to be determined.

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7.14 Single photon emission tomography - There are a few published studies using functional neuroimaging techniques such as single photon emission tomography (SPET) in CFS.¹³¹⁻¹³⁶ Studies to date have used inconsistent case definitions,

resting scans, poor resolution SPET scanners and semi-quantitative methods to detect changes in regional cerebral blood flow (RCBF).¹³⁷ The most widely publicised study found that brainstem perfusion was significantly reduced in CFS subjects compared to controls, with depressed patients showing intermediate values.¹³⁴ However, other groups do not report brainstem perfusion values because of the technical difficulties of imaging this small structure.

Any interpretation of this finding must await its independent replication.¹³⁷

7.15 In the current studies using functional neuroimaging, confounding by such factors as levels of arousal, depression, anxiety and medication are important but are not always considered. No studies have yet used activation tasks (a scan taken during the performance of a standardised test). Results have been inconsistent. In general the application of the dynamic neuroimaging to complex conditions such as CFS has happened in advance of establishing the full range of normal variation within the population. Even in such a small literature variations in results are already observable, and it is at present impossible to come to any firm conclusions. We endorse the conclusion of the most recent study that 'findings are neither sufficiently sensitive nor specific to allow its use as a diagnostic tool, although it may have a role in understanding the pathophysiology of the disease'.¹³⁵

7.16 Even with improved methodologies, problems will remain in interpreting SPET studies, as is the case in established fields such as schizophrenia research. It is difficult to determine whether any deficit in RCBF in response to the task is the cause or result of the performance deficit.

7.17 SPET and PET are relatively invasive procedures involving exposure to radioactive agents. There is no justification for their use outside carefully conducted research. Such research is needed.

7.18 Another area of current interest is the role of possible neuro-endocrine dysfunction in CFS.¹³⁸ A well conducted study using dynamic tests suggests subtle abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis¹³⁹ reflected in abnormal responses to neuro-endocrine challenge tests.^{140,141} The possibility that previous depressive illness alters the reactivity of the HPA axis to subsequent infective or psychosocial stress is intriguing. The suggestion that a subgroup of CFS patients is characterised by persistent low cortisol levels (in contrast to major depression) is being investigated by two controlled trials of replacement therapy. This is an area of great interest, although it is too early to draw any conclusions.

7.19 We keep an open mind regarding these findings. Similar effects have been noted in many conditions, some of which overlap with CFS. These include eating disorders, post-traumatic stress disorder, seasonal affective disorder and fibromyalgia. A number of important confounders exist, such as sleep disturbance, depression and anxiety, all of which are relevant to CFS. A recent study was able to mimic the endocrine abnormalities observed in CFS in healthy night-shift workers.¹⁴²

7.20 It remains possible that any observed neuro-endocrine abnormalities in CFS may be epiphenomena of the clinical condition, or related to the confounding effects of psychological distress, sleep deprivation or prolonged inactivity. There is no current evidence that such disturbances are causative, and at present no evidence that correcting them is of benefit.

7.21 CFS patients frequently complain of considerable difficulties with memory, attention and concentration. There have been at least 15 studies of cognitive functioning in CFS published to date.^{127,143-157} We find that the results of neuropsychological testing are inconsistent. Selective attention and complex

neuropsychological functioning may be impaired, but overall the results generally do not reflect the severity of the subjective complaints encountered.

10,158,159 Confounders such as sleep disturbance and mood disorder are relevant, particularly to complaints of impaired memory and concentration.158, 159

Summary

- CFS cannot be considered either 'physical' or 'psychological'-both need to be considered simultaneously to understand the syndrome.
- The depression which is found in half of patients cannot simply be regarded as secondary to the disability and uncertainty associated with CFS.
- The number of psychiatric symptoms increases with the number of somatic (bodily) symptoms - the most severe forms fulfil criteria for somatisation disorder, in which disability is profound.
- Structural and functioning neuroimaging and neuro-endocrinological investigations have not led to consistent abnormalities being demonstrated in CFS. More clearly established normal variations are necessary to interpret the observed abnormalities. These may be relevant to some sub-groups, but may also be due to such confounding factors as sleep disturbance and prolonged inactivity.
- Current findings in relation to muscle dysfunction and immune abnormalities are open to several interpretations. There is no compelling evidence for a substantial primary role of neuromuscular dysfunction.
- Reports of cognitive abnormalities are similarly inconsistent. Further research is needed in all of these areas.

CHAPTER 8

Presentation, assessment, investigation and prognosis

8.1 At the core of CFS is the concept of easy fatigability: profound fatigue, which is made worse by minimal physical or mental exertion.

8.2 Attempts have been made to list symptoms that are 'key features' or 'typical' of CFS.10 All are symptoms that can be encountered in those who also fulfil the operational criteria for CFS, but all can also be encountered in other conditions, physical or psychological.

8.3 There are no diagnostic abnormal physical signs in CFS. Some patients complain of a sore throat, but clinical pharyngitis is unusual. Some patients experience painful or tender lymph glands. Clinically significant lymphadenopathy should not be accepted as part of CFS-instead a cause must be sought. A history of low grade fever is sometimes given, but patients with a confirmed fever of >38 C should be investigated to exclude alternative diagnoses.

8.4 Features such as muscle wasting, orthostatic hypotension, facial pallor, breathlessness and tremor are not specific physical signs of CFS, but may reflect prolonged inactivity and/or anxiety disorders. If pronounced they may indicate other diagnoses.

8.5 Although patients do complain of muscle pain (myalgia) and subjective weakness, there is no evidence of muscle contractile failure or abnormal neuromuscular fatigability once the effects of inactivity are taken into account.

8.6 Patients with CFS need to be assessed using a biopsychosocial approach.10, 160 There are a number of difficulties in achieving this in practice. Some doctors and some patients resist the requirement that biological and psychosocial aspects need

to be assessed with equal thoroughness. The organisation of medical clinics places emphasis on technological investigation to discover possible physical illnesses and it may hinder the investigation of psychological problems, which require private, quiet interview facilities.⁸ Many GPs wishing to refer have only the option of either a referral to a mental health team (which many patients resist) or to a general medical, endocrine or infectious disease clinic, which may be ill-equipped to offer a biopsychosocial assessment.

8.7 Primary care offers a better opportunity for a biopsychosocial assessment. Throughout this report we emphasise the importance of early treatment in primary care to develop a beneficial therapeutic doctor-patient relationship and to attempt to prevent chronic disability. There are still problems and mutual misunderstanding.¹⁶¹ We are aware of claims that some doctors still dismiss the patient's symptoms with such phrases as 'Pull yourself together'.

Specific training of doctors may therefore be required to understand and manage these disorders.⁸

8.8 In view of the large number of diagnostic possibilities in patients who present with a self-diagnosis of ME or symptoms suggestive of CFS, the doctor must be alert to a wide range of possible diagnoses. In assessing patients with excessive fatigue it is important to strike a balance between under- and over-investigation. There is all too often a tendency for possible physical illnesses to be over-investigated and possible psychological disorders to be under-investigated. The need for investigations will be determined largely by the results of a good clinical history, physical and psychiatric examination, all of which are mandatory.

8.9 Unless there are pointers in the history or examination, detailed laboratory investigation is largely unhelpful in anyone with fatigue lasting more than six months.¹⁶² This has been found in both primary ^{52,36,163,164} and specialist care.¹⁶⁵ The highest observed prevalence of alternative physical diagnosis is only 5%.⁴⁹ Studies of selected samples of patients have revealed changes in some parameters, such as antinuclear factor, immune complexes, cholesterol, immunoglobulin subsets and so on; these are encountered only in a minority, are rarely substantial, and do not lead to any particular form of clinical management. Their significance is for researchers rather than clinicians.¹⁶⁶ There are no laboratory tests that establish or confirm a 'diagnosis' of CFS, and none should therefore be performed for that purpose.

8.10 The following simple tests are a sensible compromise between under- and over-investigation¹⁶²

- full blood count
- acute phase protein changes (ex ESR, CRP)
- liver function tests
- urea and electrolytes
- TSH and free thyroxine
- creatine kinase
- urine test for protein and sugar.

8.11 We reiterate the sentiments of a previous report from the Royal Colleges of Physicians and Psychiatrists⁸ and once again draw attention to the inappropriateness of the typical 'linear logic' applied in the medical management of illnesses such as CFS and many others. The system by which all likely medical causes are first excluded, including remote possibilities, and then belated

consideration given to social and psychological factors, is inefficient, expensive, illogical and at variance with the known risk factors for such conditions.^{8,162,167}

8.12 The aims of assessment for patients presenting with symptoms suggestive of CFS may be summarised as follows: ^{8,168,169}

1. to clarify the nature of the complaint and consider alternative diagnoses,
2. to assess the current disability,
 3. to elicit the beliefs and fears of patient and family about symptoms, diagnosis, and treatment.
 4. to elicit the beliefs of patient and family about the role, benefits and consequences of rest and activity,
5. to identify psychological distress,
 6. to formulate the problem in terms of predisposing, precipitating and perpetuating factors, and
7. to provide a basis for negotiating a management plan.

8.13 It is still too early to comment on the prognosis of CFS, because of the relative paucity of long-term studies, the lack of comparability of samples, and the frequent absence of good clinical practice in the management of long-term disability.

8.14 The prognosis for patients with the label of ME who reach specialist care is of concern. Behan & Behan wrote that 'most cases do not improve, give up their work and become permanent invalids, incapacitated by excessive fatigue and myalgia'.¹⁷⁰ Of those seen in a Seattle clinic, 60% were the same or worse two years later.²³ Only 18% of those referred to a Belfast clinic improved,¹⁷¹ and 13% of those seen in an infectious disease clinic in Oxford considered themselves fully recovered two years later, although more had improved.⁵⁴ Of subjects who had taken part in treatment studies in Australia, 6% had fully recovered at three years.¹⁷² These results suggest a poor prognosis in some patients. However, as this is almost certainly influenced by selection factors it sheds no light on the natural history of CFS.

8.15 No laboratory markers, virological or immunological, predict outcome.^{23, 172}

8.16 Several studies suggest that poor outcome is associated with social, psychological and cultural factors. These include the strength of belief in a solely physical cause for symptoms, untreated psychological distress, and the use of avoidant coping strategies (such as reducing activity and/or dietary, social and other restrictions).^{23,54,55,172,173}

8.17 No evidence for any structural or progressive pathology exists for CFS. There is no evidence for any excess in mortality, with the important exception of suicide, which deserves further research. Chronicity is likely to be associated with perpetuating factors, which may include poor illness management, inadequate rehabilitation or unaddressed psychosocial issues. We therefore urge that no one should be regarded as permanently impaired until they have had the opportunity of participating in all sensible efforts at rehabilitation.

Summary

- Profound fatigue, made worse by minimal physical or mental exertion, lies at the core of CFS but there are no other cardinal features, abnormal physical signs or laboratory tests which can confirm the 'diagnosis'.

- Biopsychosocial investigation is essential and is best provided in primary care. Secondary care units should provide facilities for such assessments when required.
- Unless there are atypical features, limited investigation for alternative diagnoses is appropriate and should be accompanied by assessment of patients' disability, psychological state and illness beliefs.
- The prognosis for patients seen in specialist care is of concern, particularly for those who are untreated.
- No one should be regarded as permanently impaired until they have had the opportunity of participating in all sensible efforts at rehabilitation.

CHAPTER 9

Management

9.1 In our review of the subject of CFS nowhere did we find as much disagreement as in the area of management. We will therefore draw attention first to those areas in which consensus and/or sound research exists. This evidence is largely confined to specialist settings - there is a pressing need for primary care based research.

9.2 Management is usually preceded by diagnosis, which should, naturally, be as accurate as possible. However, the issue of diagnosis is an exceedingly complex one. In the current climate there are advantages and disadvantages to making a diagnosis of CFS. We have concerns, developed below, about the dangers of labelling someone with an ill-defined condition which may be associated with unhelpful illness beliefs, and also lead to therapeutic nihilism. On the other hand we are also aware of the need for a diagnosis in the clinical situation, and the very real dangers of delegitimising a patient's predicament and distress.^{174,175} Without a diagnosis it may prove impossible to organise dealings with family, friends and work.¹⁷⁶ At present a diagnosis of CFS, like that of fibromyalgia or irritable bowel syndrome, can be of use in clinical practice as a structure for patient understanding and a model for treatment.¹⁷⁷ Hence, rather than give premature guidance on when, or even if, to use the diagnosis of CFS, it is more essential that if a doctor chooses to use the label he or she must be also able to give appropriate management. Whatever label is chosen it is essential that the doctor accepts the patient's distress as genuine. No patient should ever feel their credibility is doubted. The doctor needs to encourage the patient to assume responsibility for recovery, but this must be done without implying guilt or culpability for becoming ill in the first place. There is no place in the clinical consultation for such statements as 'there is nothing wrong with you' or 'it is all in the mind', just as there is no place for such statement as 'you have ME - there is nothing I can do'. A doctor may have doubts about the nosological status of CFS, but it is unacceptable and counterproductive to add this scepticism to the distress of chronically fatigued patients.

9.3 We emphasise the crucial role played by the doctor-patient relationship and such factors as trust, expectation, courtesy, hope and the therapeutic alliance. Doctors' efforts in this endeavour may, occasionally, be threatened by the patient who produces literature indicating that the symptoms are unlikely to respond to current management.

9.4 There is reasonable consensus that good clinical management relies on the biopsychosocial approach.^{10,160} The doctor should give relevant information, take a problem-solving approach, look at coping strategies and use a multidisciplinary approach. We advocate that depression or anxiety, when identified, should be treated.¹⁰

9.5 We strongly reaffirm that cautious, controlled increases in activity remain the corner stone of the management of CFS. Overcoming the consequences of reduced or variable levels of activity by a programme of controlled increase in activity, often over a time-scale measured in weeks, is a crucial part of good clinical care.^{10,169,178} There are a number of ways in which this can be achieved. Simple exercise programmes are used in a number of centres. A recent randomised controlled trial of graded exercise was successful,¹⁷⁹ whilst a second trial also showed benefits for those who completed the programme, although the intention to treat analysis revealed problems with the acceptability of treatment.¹⁸⁰ In fibromyalgia, randomised controlled trials have shown that exercise is both safe and beneficial.¹⁸¹ There is no evidence that exercise leads to permanent damage or disability in CFS.^{178,182} Instead, exercise should be chosen in the light of the patient's current capabilities, based on knowledge of the degree of physical unfitnes and deconditioning.

Goal setting is an important part of management: such goals 'should be realistic, achievable and should be increased in a stepwise manner'.^{10,183,184}

9.6 We draw particular attention to the need for increases in activity to be planned in a cautious, controlled and mutually agreed manner. Over ambitious or aggressive exercise programmes, or following advice to 'exercise away the fatigue' are likely to fail. This can be understood in the light of current knowledge of exercise physiology and neuromuscular response to unaccustomed activity, and does not imply any pathological process specific for CFS.^{95,185, 186} In our experience many CFS sufferers adopt a pattern in which brief bursts of activity, inevitably followed by a worsening of the symptoms of pain and exhaustion, in turn give way to periods of prolonged rest and activity avoidance.^{187,188} This pattern may be reinforced by the sense of frustration often experienced by sufferers, and perhaps also by preexisting personality and lifestyle.

9.7 Two recent studies provided support for the frequent clinical observation that some sufferers seen in specialist centres report premorbid personalities and lifestyles characterised by a tendency to 'oversubscribe to social norms that dictate exhaustion as a way of life',¹⁸⁹ mirrored in particularly strenuous work and social lives.¹⁹⁰ Effective psychological and physical management may involve replacing a varying activity level with a consistent programme of rest and activity, avoiding extremes of both. If sufferers are warned not to attempt sudden upswings in activity, which may be associated with further fatigue and myalgia the following day, then the need for prolonged rest to relieve such symptoms may be reduced in turn. Patients should be advised that such a programme of gradually increasing activity (in which each increment may be spread over several weeks) may cause a transient (activity associated), rather than a persistent, increase in muscle fatigue and pain.^{169,184,191} Giving such information may help to reduce understandable patient anxiety about the consequence of activity, and may in turn reduce symptoms and improve compliance. Rehabilitation aims to reduce the handicapping stimulus driven cycle of CFS, in which symptoms are a signal to rest, and replace previous sensitisation by tolerance.

9.8 Another approach to rehabilitation is known as cognitive behaviour therapy (CBT), which has been applied to a number of syndromes, particularly those in which disability is multifactorial.⁹ At present two randomised controlled trials have been carried out in this country. In the first, 12 sessions of CBT were compared to standard medical care.¹⁹² Active treatment led to a satisfactory outcome in 73% of patients, compared to 27% of those receiving standard care. Improvements continued in those who had received active treatment during follow-up. A second trial compared 12 sessions of CBT with 12 sessions of relaxation therapy as a control for

non-specific effects of treatment.¹⁹³ Active treatment led to reductions in fatigue and functional disability, and again improvement continued during follow-up. In contrast, an Australian randomised controlled trial comparing six sessions of CBT with both placebo and immunological therapy showed that a benefit of CBT on self reported measures of function, but these were not maintained on follow-up, the authors concluding that CBT offered no advantages beyond those of regular medical care and follow-up.^{194,195} In a previous pilot study of 50 patients, problems were encountered in recruitment and compliance,¹⁹⁶ but these difficulties were not encountered in three subsequent controlled studies.¹⁹²⁻¹⁹⁴

9.9 CBT is a promising and cost-effective approach that has been recommended for the outpatient management of CFS,¹⁹⁷ although up to 12 sessions may be required. The treatment is safe and acceptable. The main drawback is lack of access to trained personnel. We are aware that many clinicians already use elements of this approach in their routine clinical practice.^{19, 200}

9.10 We point out that these therapeutic approaches do not involve, as some believe, a shift from an exclusively physical view of CFS to an exclusively psychological model. This would be both impractical and inappropriate. Instead the purpose is to broaden, rather than confront, patients' beliefs and behaviours in order to encompass a wider range of possible explanations for continuing ill health, and hence a wider range of treatment options.^{169,184,191}

9.11 We are aware of the frequent misgivings and misconceptions that continue to surround the subject of activity, exercise and rest in CFS and that anecdotal experiences sometimes appear to contradict this approach. It is essential that in planning treatment doctors are aware of these misgivings, particularly since a good doctor-patient relationship requires that the patient feels understood by the doctor. In this context the doctor must sympathise with the patient's complaint of extreme fatigability, but must take care always to encourage co-operation, but not collusion. The prevention of disability, particularly in primary care, requires encouragement to be active. Prolonged rest is known to be associated with secondary disability (vide infra). We are therefore concerned about such advice as the need to reorganise life to avoid unnecessary pressure, or to 'listen to your body'.¹⁰ This appears to endorse the advice often given to sufferers to 'live within your limits', which carries a risk of perpetuating disability. 'Listen to your body' is probably equivalent to what psychologists call 'symptom monitoring', and is one of the ways in which disability can be perpetuated in many conditions with both physical and psychological components.²⁰¹ We can find no evidence to support such advice.

9.12 We have similar concern about 'helping patients to come to terms with losses which are consequences of disease'.¹⁰ In our experience such advice is only applicable to a very small minority of patients - for the majority it runs the risk of colluding with disability, and reinforcing the erroneous view that CFS is associated with permanent structural damage. For similar reasons, in the absence of better information on training and evidence of efficacy, we have concerns about the recent growth of 'counselling' for CFS sufferers.

9.13 We emphasise the deleterious effects of unproven illness beliefs such as the fear that any activity which causes an increase in fatigue is damaging - that 'doing too much' causes permanent muscle damage and that CFS is irreversible or untreatable.²⁰² Research suggests that catastrophic or dysfunctional beliefs are common in CFS patients and are related to disability.

^{203,204} Such inaccurate beliefs might fuel avoidance of activity, and then be powerfully reinforced by the pain and fatigue which inevitably follow each attempt to resume previous levels of activity. This in turn might lead to increasing restriction of activity, frustration, loss of control and

demoralisation.163,201,202 Using avoidant strategies to cope with chronic fatigue has been associated with worse disability.202,203,205

9.14 There is also anecdotal opinion suggesting that rehabilitation needs to take account of the 'stages' of illness,¹⁰ which usually implies that during 'active' phases of illness patients need to restrict their activity. We know of no evidence to support this. Intuitively the approach seems reasonable, but we still sound a note of caution. Studies on back pain show that early use of rest as a coping strategy worsens disability, whilst the only controlled trials of which we are aware suggest that early exercise after a proven viral illness is not only safe, but beneficial.^{206,207} Thus whilst encouraging rest in the early stages seems sensible, we need evidence before endorsing this, and draw attention to the possible adverse effects.

9.15 We emphasise the vast literature on the adverse effects of rest, that can be found in literatures ranging from physiology, sports science, aeronautics, neurology, ergonomics, psychology and general medicine.^{105,208-211} We believe that rest per se is contraindicated in CFS. If it has a role, it is only as one component of a strategy for a short period, measured in days or weeks.

9.16 We make similar observations about the role of sleep. Sleep disturbance is common in CFS, and may play a role in the development of symptoms.²¹² Experimental sleep deprivation can reproduce many of the symptoms of CFS.²¹³ Promoting healthy sleep is certainly justified.²¹⁴ However, excessive sleep can lead to similar symptoms, including fatigue, headache, exhaustion, poor concentration, myalgia and others.²¹⁵

9.17 Most, perhaps all, sufferers make significant lifestyle changes as a result of illness. These may include altering their response to stressful events, adjusting their work and leisure goals, altering their coping strategies, and reassessing their priorities and values.^{189,216} These need to be acknowledged, and often encouraged. However, this must be seen in the context of encouraging recovery and preventing relapse, rather than reinforcing further withdrawal.

9.18 In summary, we are aware of no evidence in favour of strategies promoting avoidance in CFS, such as advising avoiding activity, promoting rest and accepting limitations. In contrast to the absence of any evidence supporting these strategies, there are many cogent reasons, supported by evidence, why such advice may be illconceived.

9.19 Self-help literature has been insufficiently assessed. We are aware of only one randomised evaluation of self-help literature - a preliminary report²¹⁷ which suggests some benefit²¹⁸ and is aimed at individuals with chronic fatigue presenting in primary care. We would like to see randomised trials of different styles of selfhelp/advice. We have a number of concerns about the possible deleterious effects of parts of the self-help literature currently available to sufferers, and in particular those aimed at children and families.

9.20 We have concerns about the use of complementary therapy and dietary interventions, echoed elsewhere.¹⁰ As yet none have been proven effective,²¹⁹ whilst the results of those that have been studied have not been encouraging.

220-222 We believe the effects of complementary therapies are hard to distinguish from those due to the charisma of the practitioner. The popularity of alternative approaches may stem from the recent observation that the general public perceives orthodox medicine as particularly ineffective in the management of chronic fatigue.²²³

9.21 We conclude this section by stating that the management of CFS involves co-operation, but not collusion; the avoidance of excessive rest and excessive sleep; the

gradual controlled increase in activity; awareness of the dangers of labelling; and awareness of the role of patient anxiety.

9.22 The list of treatments for which therapeutic claims are made in the context of CFS is a source of concern. There is no systematic evidence supporting any drug regime for CFS.^{10,169,214}

9.23 We see no role for immunoglobulins, antihistamines or other immunotherapy. There is no compelling evidence linking immune dysfunction with disability,²²⁴ and no convincing evidence that any agent is effective.²²⁵⁻²²⁷ Antiviral agents are not indicated.²²⁸ Experimental treatments such as immunotherapy should be given only as part of controlled clinical trials. We see no role for vitamin or dietary supplementation, and are unconvinced by the efficacy of magnesium or evening primrose oil.

9.24 Antidepressants are used by a variety of clinicians involved in the care of patients with CFS. At present most of the favourable evidence comes from uncontrolled studies.²²⁹⁻²³¹ Two placebo-controlled studies of fluoxetine are inconclusive - one finding evidence of efficacy,¹⁸⁰ the other finding no such evidence.²³² A short study using phenelzine suggests monoamine oxidase inhibitors deserve further assessment.²³³ At present we continue to endorse the use of antidepressants in the many CFS patients with depression, since there is a wealth of clinical trials supporting the use of antidepressants for depressive symptoms in other contexts.

We note positive evidence from well-planned trials and systematic reviews supporting the use of antidepressants in such conditions as chronic pain, premenstrual syndrome and fibromyalgia. We draw attention to the need for further controlled clinical trials of antidepressants in non-depressed CFS patients before making a recommendation. We are also unable to make any recommendations about the choice of antidepressant without further evidence.

Summary

- Acceptance of the patient's symptoms and establishing a therapeutic alliance are the starting points of effective management of CFS.
- Gradual, planned, mutually agreed and monitored increase in exercise forms the cornerstone of treatment. Excessive rest and the pattern of alternating over- and under-activity are counterproductive.
- CBT has been shown to be effective in recent controlled trials. Antidepressants should be used in patients with depressive disorders.
- Some patients need help to adjust their previous hectic lifestyles to one of consistent and more moderate levels of activity.

CHAPTER 10

Children and CFS

10.1 The subject of CFS and children appears to be a particularly emotive one.

^{10,234} The general approach taken to the subject of CFS and children is, in our view, similar to that in adults - though there are fewer experimental findings upon which to base recommendations.

10.2 CFS in children is a complex issue. Marcovitch²³⁵ and others²³⁶ draw attention to the need to address the problem in 'not just physical, but also in emotional, social and family terms', a point we endorse strongly. CFS in children covers a broad spectrum of problems, ranging from the minor to the very serious, perhaps even involving the Munchausen's by Proxy syndrome.^{235,237}

10.3 CFS does occur in children and adolescents. There is no firm information on the prevalence, although we suspect that, as in adults, estimates based on the numbers seen in secondary or tertiary paediatric centres are likely to underestimate prevalence whilst overestimating severity and duration. We are unaware of any evidence that severe forms are more common in children than adults. Epidemiological evidence in children is needed.

10.4 We see no need for separate CFS criteria or a diagnostic scoring system for children, as has been suggested.¹⁰ In our experience the Oxford criteria²⁰ can be applied to children without difficulty and with only minor modifications. The symptoms encountered in children are similar to those in adults. The only point of divergence between children and adults is that six months duration criterion may be too long - three months may be more appropriate. We have frequently encountered children with a shorter illness duration. It is our impression that early intervention in these children might be particularly beneficial.

10.5 The diagnosis of somatisation syndromes presents problems in children as much as in adults. Certainly some children present with abnormal fatigue and fatigability, accompanied by many other symptoms, in whom such diagnoses may be warranted. Others may present with abdominal pain or headache. Such children should not be diagnosed as suffering from CFS if they do not meet the criteria.

10.6 There is a literature on CFS in childhood, albeit an unsystematic one. This literature, based almost entirely on selected samples, has a strong psychosocial flavour, which we suspect reflects the consensus view of paediatricians, who themselves see selected samples. It has been argued that CFS in children is associated with somatisation,²³⁸⁻²⁴⁰ depression²⁴⁰⁻²⁴² and even bipolar disorder.^{243,244}

10.7 The symptom of depression is certainly important and common: according to Bell, 60-80% of children with CFS describe depression among the symptoms,²³⁶ although self-harm seems unusual. As with adults, emotions such as frustration are encountered, together with feelings of loss related to time away from school and impairment of social relations. Anxiety is also common. Many children attending specialist centres with a diagnosis of CFS are indeed high achievers, and in consequence often have anxieties about their school performance, which cause them to work excessively hard to achieve at the limits of their ability. Overall we believe that relevant psychological factors contributing to CFS in children are not usually clearcut psychopathological risk factors such as abuse, but instead may involve a complex family dynamic of involvement, high expectation, limited communication on emotional issues and previous experience of illness.²³⁸ We also emphasise that such factors may only be relevant for those children with severe disability - studies of less severely affected children in primary care are needed.

10.8 School phobia is important, both as a differential diagnosis and a complication of CFS. The wish to resume school attendance does not exclude the diagnosis - children, including those with CFS, may have profound anxieties about attendance despite a strongly expressed wish to resume schooling. The diagnosis should be made if there is established phobic fear and avoidance of attending school. Like every medical diagnosis it is neither a label nor an insult.

10.9 It is important to appreciate the validity of the child's complaints.¹⁰

Children are as, if not more, sensitive to any suggestion their ill health might be spurious, or 'all in the mind'. Acknowledging the reality of the child's symptoms reduces the risk of a defensive reaction by either the child or family.²⁴⁵ Thus although exploration of family and psychosocial issues is always indicated, this must always be done with tact and sensitivity,²³⁵ especially as many families continue to see the problems as solely 'organic'. ²⁴⁵ Obtaining any history of similar illnesses in the parents' biographies can also be important.

10.10 As in adults it is essential that a full clinical history and physical examination is performed in every case but the number of physical investigations should be kept to a minimum unless there are specific pointers in the history or examination. Laboratory investigations are usually unhelpful, with the exception of tests for infectious mononucleosis.^{235,240,241} Tests for the heterophile antibody (eg Monospot or Paul Bunnell) may be useful for screening, but do not diagnose either EBV infection or CFS. EBV infection can only be diagnosed by the presence of the VCA IgM antibody. Tests must be kept to a minimum, remembering however that they can serve to reassure families about the absence of sinister pathology thus allowing rehabilitation to proceed. When 55 children with chronic fatigue were fully evaluated in one centre, only one alternative diagnosis (sinusitis) was discovered.²⁴⁵ We deplore the statement that SPET scanning can be helpful in children.¹⁰ At present we see no role for this technique in children. A framework for assessment and investigation of CFS in children is summarised in Table 2.

Table 2: Assessment and investigation of CFS in children

Presenting complaint:	Principal symptoms including: sleep patterns; length of illness; time missed from school; withdrawal from activities (typical day)
Past medical history:	Previous illness and course of recovery; illness behaviour; allergic history
Family history:	History of illness in other family members; illness behaviour - family adaptation to current illness; description of family relation-ships; previous adverse experience of doctors
Social history:	Usual activities; peer relationships; degree of independence; school performance; enjoyment of school
Illness history:	Previous treatment and treatment experiences; child and family beliefs about illness and effect of activity; dietary habits and beliefs.
Mental state:	Anxiety, depression, school phobia
Investigation:	As for adults. Do not over-investigate.

10.11 No systematic evidence exists on appropriate management in children. We will therefore outline what we consider to be good clinical practice, views that are supported in case studies and case series, whilst noting that such reports are usually of children with considerable disability and illness durations. In such samples we note the success of behavioural activation packages,²⁴⁵⁻²⁵⁰ often linked with a family therapy approach.^{251,252}

10.12 As far as possible we discourage home tuition - in the largest series to date if the children were no longer in school immediate return to school was encouraged.²⁴⁵ Tuition at home should be reserved only for the most severely affected and should be for as short a time as possible, and always in close liaison with the school.

10.13 Involvement of the parents is naturally vital, because treatment failure may happen when the parents remain convinced that active rehabilitation would be

harmful.²⁴⁸ Family issues are important. Sometimes one member of the family, usually the mother, has given up work to look after the child, leading to a fixed sick role which can be difficult to alter. Existing family characteristics such as over protectiveness can be exacerbated. The loss of peer group contact reinforces the dependence of the child on the family.²³⁸ Work with the family and liaison between health and education services is almost invariably required.²⁵³

10.14 We also draw attention to the relevant statutory duties imposed on medical practitioners by the School Attendance Act and the Children's Act, and the need to be prepared to act in the best interest of the child if these are being breached.

10.15 A recent paper reported the outcome of a case series of 50 children with severe chronic fatigue, most of whom recalled a triggering symptomatic infection. A programme beginning with careful assessment and engagement, followed by symptomatic relief, reduction of secondary gain, insisting on regular school attendance and the gradual resumption of activity despite ongoing fatigue resulted in a good outcome in 94%.²⁴⁵ Such findings are uncontrolled and based on selected cases, limiting the conclusions that can be drawn, but do contradict unsupported statements such as 'the average length of illness in teenagers lasts about four and a half years.'²³⁴

10.16 As with adults we again note that most children ought to be adequately managed by a combination of primary care, school nurse and school authorities, together with the support of local paediatric, psychiatric or psychology services where appropriate. Referral to a specialist team may be indicated if there is evidence of specific psychiatric disorder, severe or prolonged disability, or family factors interfering with progress. In the absence of such factors basic management involves reassurance, explanation, exploration and alleviation of school factors (learning difficulties, exam stressors, bullying), basic goal setting and monitoring with planned increases in activity and planned return to school. These can usually be provided by the GP or primary care team, who will need to monitor the child and family at least weekly. The team needs to be vigilant for the occasional individual who slips into chronic invalidism and school refusal.

10.17 In our opinion good clinical practice for severely affected children will almost invariably involve access to a combined unit. Some children may have been debilitated for a prolonged period and require admission to a specialist unit with facilities for assessment, treatment and rehabilitation. Such units will require close co-operation between paediatricians and psychiatrists. The necessary skills may involve psychology, occupational therapy, nursing, physiotherapy, dietetics and education. Particularly at the beginning of treatment considerable input of resources is needed to engage the family and support them through a period of change. Attention to staff morale and dynamics is important - such 'paralysed' children can occasionally 'paralyse' staff, so staff cohesion and support should not be neglected.

10.18 Set out below are some details of our consensus views on good practice in rehabilitation:^{235,245,248,253}

1. Ascertain current levels of functioning.
2. Complete a timetable with child and family to establish clear periods of eating, rest and activity in the day.
3. Start at the child's current level of activity, with small (5%) increases each week. Stress the need to go at an agreed pace-not too fast and not too slow. As the child's tolerance improves the increases in level of activity can be more substantial.
4. Activity might include:

- graded exercise programme as arranged by physiotherapist or easily monitored exercise, eg walking
 - mental activity, eg reading
 - school activity
 - social activity
5. Identify goals for each week with child and family.
6. Review goals at the end of each week, clarifying whether or not they have been achieved, discuss what was difficult for the child and what was easy, then set goals for the next week.

10.19 We note that some children labelled as having ME are managed in isolated units which do not usually function as tertiary referral centres and cannot provide the combined skills of the multidisciplinary team. Whilst individual commitment and enthusiasm are important, paediatricians working in such units need to interact closely with multidisciplinary teams so that the appropriate range of paediatric, psychiatric, social and educational skills can be used in the child's management and outcome audited.

Summary

- The presentation and management of CFS in children is similar to that of adults. The criteria for CFS may be shorter than adults. Early rehabilitation is particularly important.
- Multi-professional care is appropriate especially for more severe problems.
- There are fewer systematically acquired data in children than adults with CFS and more research is required.

CHAPTER 11

Future research

11.1 It is not within our remit to define a research agenda, though this brief review has indicated where further research is needed. We are satisfied that the normal processes of supporting sound research are adequate in this respect. The Medical Research Council and the major medical charities have supported, and continue to support, CFS research.

11.2 Whatever research is undertaken, the need for careful attention to methodology is clear¹⁰ This includes the use of adequate case definitions, careful descriptions of samples, the routine use of psychiatric screening instruments to allow stratification, and the use of appropriate clinical outcome measures.

11.3 We note the current enthusiasm for research into neurobiological aspects of CFS. We share that enthusiasm, provided that the appropriate methodological rigour is sustained. We have doubts about the indiscriminate use of complex technologies such as neuroimaging in a heterogenous and ill-defined group of patients, in whom there are also many confounders, such as duration of illness, sleep disturbance, depression, drug therapy and so on. We draw attention to the fact that 'normal' population variation in many of these tests, particularly the newer neuroimaging techniques, remains poorly defined.

11.4 We particularly emphasise the need for controlled clinical trials of therapy.^{10,169} In our view many, if not most, of the treatments currently advocated

for CFS should only be used in a controlled setting. This will lead to a rapid increase in knowledge. Trials in primary care are a particular priority.

11.5 The issue of sickness and disability benefits is understandably controversial, albeit beyond our brief. We understand that the Benefits Agency is considering this topic separately. However, the extent, purpose and outcome of benefits should also be considered a suitable topic for research.

CHAPTER 12

Facilities and service provision

12.1 Overall we strongly emphasise that the management of CFS is first and foremost the responsibility of the primary care team. We see no reason for the creation of specialist units for the majority of cases.²⁵⁴ Instead we believe that the majority of cases can be managed satisfactorily in primary care provided that:

- a) the GP has sufficient understanding of, sympathy towards and skills necessary to manage the condition,
- b) that other members of the primary care team (physiotherapist, social worker and/or psychologist) can be involved when necessary.

12.2 Nevertheless, as with many conditions, a small number of patients may develop severe, prolonged or complex disabilities that require specialist care. We agree with others who suggest that this is an area of unmet need, which we see as broader than the narrow perspective of CFS. This would include the field of chronic functional symptoms and syndromes, such as irritable bowel, fibromyalgia, noncardiac chest pain, chronic pain and others. All these syndromes, which undoubtedly overlap, are associated with morbidity and high resource consumption. Their management is unsatisfactory for both doctor and patient.^{5,255} There is a need for a reconfiguration of general hospital services to address these problems more effectively and efficiently.

12.3 We therefore urge that service provision for CFS combine a physical and psychological multidisciplinary care approach. There are a number of models for delivering such care,^{169,256} but all involve some form of multidisciplinary working, and all involve some form of rehabilitative management strategies. Relevant personnel usually come from general or specialist medicine, psychiatry, psychology, social work, physiotherapy, behaviour and occupational therapy. Issues of skills and training have already been addressed in the joint Royal Colleges' Report⁸ (pages 12 - 14: Chapter 3; pages 29-31; Appendices B and C) and elsewhere.²⁵⁶ Table 3 gives what we consider the essential skills necessary for the task.

Table 3: Essential skills/tasks for a multidisciplinary CFS unit.

1. Ability to take a full history and carry out an appropriate physical examination
2. Ability to obtain information on emotional issues such as depression, anxiety hopelessness and suicide risk
3. Ability to obtain information on attributions, coping strategies and previous experiences of treatment
4. Perform the minimum number of investigations

5. Provide appropriate and unambiguous reassurance when there is no evidence of relevant physical pathology
 6. Provide appropriate and acceptable alternative explanations for symptoms such as pain, fatigue, dizziness, etc.
 7. Ability to plan individually tailored rehabilitation programmes aimed at increasing activity, improving confidence and restoring control
 8. Know when and how to obtain specialist psychiatric/psychological opinions
 9. Ability to provide outcome data
-

12.4 We do not think that specific guidelines on the management of CFS should be issued for general practitioners at present. Appropriate clinical practice is not to be defined by special interest groups, nor consensus conferences, but should be based on methodologically sound research, of which there is a paucity in primary care. In the future it may be necessary to issue such guidelines for general practitioners, particularly as we advise that most of the management of CFS should occur in primary care. However, such guidelines must rigorously follow the principles of evidence-based medicine necessary to produce valid clinical practice guidelines.

12.5 Severely disabled or chronically ill patients require access to a multidisciplinary assessment and rehabilitation facility. This will allow GPs to refer such patients for a second opinion regarding any possible undetected physical illness and for benefits of a specialised, multidisciplinary rehabilitation facility. Such an assessment would usually be appropriate before declaring someone to be chronically disabled.

CHAPTER 13

Conclusions

13.1 The background to this report is the request by the CMO to the Academy of Medical Royal Colleges to produce a report on chronic fatigue syndrome concerning diagnosis, clinical practice, aetiology and service provision. This report refers, in part, to the Westcare report on Chronic fatigue syndrome (CFS), post-viral fatigue syndrome, myalgic encephalomyelitis.¹⁰

13.2 CFS is a substantial problem for patients, families and society. There is consensus on the importance of a biopsychosocial approach to aetiology, assessment, and treatment and the need for further research.

13.3 Recent findings from epidemiological and treatment studies which clarify previous points of uncertainty and potential dispute. The prevalence of CFS in primary care is between 1% and 2%, falling to between 0.3% and 0.7% if psychological disorders are excluded. Previous studies have counted people with ME, but these studies reflect those who seek treatment rather than those who suffer the symptoms. No characteristic occupational or social class distribution has been identified.

13.4 This report uses the term 'CFS' because there are recognised criteria for definition. We urge others to do likewise. The term ME is widely used but not precisely defined. We do not recommend use of this term in research or clinical practice.

13.5 The definitions of the criteria for CFS do not constitute a diagnosis

-there may be several different routes to this symptom complex. The conceptual model of CFS needs to be changed from one determined by any single cause/agent to one in which dysfunction is seen as the end stage of a multifactorial process. Although it is important to recognise the role of factors that precipitate the condition, greater understanding is required of factors that predispose individuals to develop the illness and those that perpetuate disability.

13.6 The relationship between CFS, viral infections and psychological disorders is still not completely understood, although recent findings have increased our knowledge. There is no evidence that infections have a primary causal role in the vast majority of cases, although they appear to precipitate the disorder in some. Previous personality factors and psychological distress appear to be more important than common viral infection per se. They may also play an important role in perpetuating disability.

13.7 The evidence for structural or functional abnormalities of brain or muscle or for a disturbance of endocrine or immune function as primary aetiological factors in CFS is currently weak. Many of the current findings may be epiphenomena related to the confounding effect of psychological distress, sleep deprivation or prolonged inactivity. Studies of this type will be more productive if they are performed on representative samples with careful measurement of psychological and somatic symptoms.

13.8 The issues surrounding CFS in children are similar to those identified in adults; but there is less research-based evidence. The principles of assessment are identical with the addition of a consideration of family and school factors. At present we consider that most children should do well with simple management strategies involving behavioural activation, goal setting and return to school. This should largely take place within primary care, with the assistance of such services as child guidance and psychology when relevant. Specialist intervention should be considered if overt psychiatric disorder (depression, anxiety or school refusal) is noted, or if barriers to recovery in the home or school are detected. A very few children may need assessment or admission to multidisciplinary specialist units. A range of skills drawn from paediatrics, child psychiatry, child psychology, nursing, occupational and physiotherapy, social and educational services will be necessary. Management of children with CFS that does not involve genuine multidisciplinary working and a commitment to physical and psychological rehabilitation should be actively discouraged.

13.9 Most patients should be managed within primary care, and not the general hospital. At present treatment should address psychological disorder, misunderstandings about the nature of the condition, avoidance of activity, exercise intolerance and sleep disorder. Recent trials of graded exercise and/or cognitive behavioural treatment indicate that these are helpful in management. Further research is needed to identify the non-responders and to examine whether they might have a different pattern of aetiological factors. The success of these trials emphasises the importance of doctors encouraging and supporting their patients while they gradually extend their activities. This runs counter to the advice, still given to many patients, that activity is harmful and needs to be restricted.

13.10 We wish to emphasise the importance of early and positive treatment in primary care with access to specialist facilities only when necessary. A small proportion will need to be managed within the secondary sector, where provision is currently often inadequate. Such provision must be appropriate, ie able to provide

multidisciplinary assessment and treatment, and be able to carry out the principles of physical and psychological rehabilitation. Such facilities may be developed along the lines given in the previous report published jointly by the Royal Colleges of Physicians and Psychiatrists Psychological Care of Medical Patients but other ways of bringing the relevant disciplines together for this purpose may be developed. We recommend that each Health Authority should identify appropriate service provision for patients with medically unexplained syndromes such as, but not restricted to, CFS. This must involve joint working between medicine, psychiatry and psychology. Such services could arise out of existing liaison psychiatry provision, or alternatively be new service developments.

13.11 Further research into the following areas should be encouraged:

- neurobiological aspects of CFS, using adequate case definitions, sample descriptions and assessment of confounders
- randomised controlled trials of treatment, especially in primary care
- management of CFS in children.

APPENDIX 1: Membership of the working group

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APPENDIX 2: Glossary

Chronic fatigue syndrome (CFS):

an operationally defined syndrome characterised by a minimum of six months of severe physical and mental fatigue and fatigability, made worse by minor exertion. Other symptoms such as muscle pain, sleep disorder and mood disturbance are common. Other common causes of chronic fatigue must be considered before the diagnosis can be made.

Cognitive behaviour therapy (CBT):

a pragmatic approach to rehabilitation using behavioural techniques to gradually and consistently increase activity, reduce avoidance behaviour and improve confidence and illness control. Cognitive techniques are used to assist patients re-evaluate their understanding of illness, combat depression and anxiety, and look for underlying patterns of thoughts and assumptions that may contribute to disability. Unlike exercise programmes targets are not chosen to improve exercise tolerance, but to restore confidence and establish regular, predictable patterns of behaviour.

Depressive disorder:

consistently depressed mood or loss of interest or pleasure for at least two weeks accompanied by four or more of: loss of energy/fatigue; appetite or weight change; sleep disturbance; poor concentration; retardation of movement; agitation; feelings of worthlessness or guilt; suicidal thoughts.

Encephalomyelitis:

inflammation of the brain and spinal cord.

Graded exercise programmes:

rehabilitation programmes in which the patient is set gradually increasing exercise targets, with the intention of improving physical stamina, reducing physical deconditioning and improving exercise tolerance.

Medically unexplained symptoms:

common symptoms such as fatigue, headache, chest pain and dizziness which occur frequently without any clear cut biomedical explanation. Such symptoms are sometimes associated with psychological disorders (qv somatisation), but are also frequently found without evidence of any defined condition.

Myalgia:

muscle pain.

Myalgic encephalomyelitis (ME):

this term originated in 1955 to describe an outbreak of unexplained illness that affected the staff of the Royal Free Hospital. It has become linked to CFS in the last ten or more years. Because encephalomyelitis is a specific pathological process not found in these patients the term should not be used.

Neurasthenia:

a term introduced to medicine in 1869 to describe an illness characterised by chronic physical and mental exhaustion, a precursor for modern CFS. Originally thought to be an organic disease of the central nervous system, and caused by depletion of the energy supply to the brain resulting from such insults as overwork or infection, it was latterly seen as a psychological condition linked to depression and anxiety. Now an archaic term, although retained in the latest International Classification of Diseases (ICD 10).

Postviral fatigue syndrome (PVFS):

a term used in this country to describe chronic fatigue syndrome apparently triggered by a viral infection. Because of the frequency of viral infections and the relative lack of any evidence implicating viral infection in most cases of CFS, the term is to be avoided unless there is clear cut evidence of a relevant infective trigger.

Somatisation:

a condition where the patient presents with a physical symptom which is attributed to a physical disease, but is more likely to be associated with depression or anxiety.

APPENDIX 3: Case definitions for chronic fatigue syndrome

CDC-1994 19	UK 20 Principal symptoms	
Principal symptoms	Severe disabling fatigue not relieved by rest affecting physical and mental functioning	Severe disabling fatigue
Minimum duration	6 months	6 months
Functional impairment	Substantial	Disabling
Cognitive or neurological symptoms	May be present	Mental fatigue required
Other symptoms	Four required	Not specified
New onset	Required	Required
Medical exclusions	Clinically important	Known physical causes of chronic fatigue
Psychiatric exclusions	Melancholic depression Substance abuse Bipolar disorders Psychosis	Psychosis Bipolar Eating disorder Organic brain disorder
	Eating disorder	

APPENDIX 4: Chronic fatigue syndrome summary for commissioners

1. A report by the joint working party of the Royal Colleges of Physicians, Psychiatrists and General Practitioners has examined the evidence relating to the prevalence, diagnosis, characteristics and treatment of chronic fatigue syndrome (CFS). This Appendix is a summary of their findings designed principally for purchasers of services.

2. In the last few years there has been a growing interest in conditions ranging from chronic fatigue, through unexplained physical symptoms and post-viral infection disorders. Collectively these have been commonly known as 'Yuppie flu'. Latterly, the term 'myalgic encephalomyelitis' (ME-see Glossary) has been used to embrace these conditions as well as a variety of psychological and physical conditions. The joint working group's report firmly dismisses the term ME on three grounds. First 'encephalomyelitis' (see Glossary) describes a distinct pathological process absent from the conditions included within the term ME. Second, the term ME implies a single diagnostic entity, which is unlikely and unproved. Third, it ignores the psychological dimension.

3. The joint working group therefore prefer the term chronic fatigue syndrome (CFS). In essence, CFS is defined by six months of severe disabling fatigue that is made worse by physical or mental exertion, and for which no adequate medical explanation can be found. It is frequently associated with somatic (somatisation- see Glossary) symptoms such as myalgia, chest pain, headache, joint pain and others. It is frequently also associated with symptoms of depression and anxiety.

4. An alternative term 'neurasthenia' is considered but not supported (see Glossary).

5. Lack of agreement about definitions and lack of methodological rigour in conducting epidemiological studies have hampered past estimates of prevalence. A number of recent studies indicate that the prevalence of CFS in primary care is

between 1% and 2%. The majority will also have co-morbid psychological conditions. The suggestion of a social class relationship, implicit in the term 'Yuppie flu', is dismissed as due to selection bias and treatment seeking behaviour.

6. Chronic fatigue syndrome is therefore widespread. A district with a population of half a million will have between 5-10,000 individuals affected at any one time. They are likely to be making in total substantial demands on primary and secondary care services. The total social and economic costs associated with their functional impairment will be considerable.

7. The report has examined available evidence on the role which viral agents may play in causing CFS. It concludes that the evidence to suggest that CFS results from the persistence in an individual of a viral agent is weak, but that there is some evidence that chronic fatigue syndromes may be triggered by specific infectious episodes. A number of viral agents, including glandular fever and viral meningitis, may be involved. However, the evidence also suggests that the likelihood of CFS is increased where there is evidence of excessive fatigue and/or psychological morbidity before acquiring an infection. Indeed, the link between infection and CFS may be a behaviour change on the part of the individual, rather than any direct linkage.

8. The report finds no consistent evidence that CFS is associated with muscle disorder save that resulting from inactivity consequent to the condition.

9. The report examines in depth the role of psychiatric disorder in CFS. Studies have consistently shown that over half those presenting with CFS have affective disorders (see Glossary) while a further quarter fulfil criteria for other psychiatric disorders chiefly anxiety and somatisation disorders (see Glossary). A fuller description of the inter-relationship between psychological and physical symptoms in patients can be found in a purchasers guide published in 1995 to accompany an earlier report published jointly by the Royal Colleges of Physicians and Psychiatrists The psychological care of medical patients: recognition of need and service provision.

10. The report lays stress on the benefits of early treatment in primary care with a view to seeking to prevent chronic disability. However, it is important that the doctor assessing a patient with excessive fatigue strikes a balance between over - and under-investigation. A good clinical history should be taken and physical and psychological examination undertaken. A simple battery of tests - full blood count, acute phase protein changes (ESR or CRP), liver function tests, urea and electrolytes, TSH and free thyroxine tests, creatine kinase and urine test for protein and sugar- are suggested to exclude other diagnoses. No diagnostic test exists for CFS, and no investigations should be performed to confirm the diagnosis, which is a clinical one.

11. The report places particular emphasis on the importance of the doctor accepting that the patients distress is genuine and being prepared to seek to treat the patient. The authors were concerned that many existing approaches to treatment are unproven or may be damaging. Neither complementary therapy nor dietary interventions have been shown to be effective, while the commonly recommended bed rest is more likely to exacerbate the patients problems. The most hopeful approaches are thought to be controlled increases in activity, such as graded exercise programmes (see Glossary), or cognitive behaviour therapy (see Glossary).

12. There is no evidence that any drug regimes are effective for CFS, though the report recommends controlled clinical trials of antidepressants for CFS sufferers with out symptoms of depression.

13. CFS in children is examined separately. The report concludes that most children can be adequately managed by a combination of primary care, school nurse and

school authorities, but that some will need to be referred to specialist units with both paediatric and child psychiatric skills as well as social and educational input.

14. CFS, as defined in the report, is likely already to be consuming significant resources in both primary and secondary care settings, much of the expenditure of no benefit to the patient and some of it positively harmful. In an area where there has been a great lack of clinical concordance the report offers the potential to improve all aspects of this situation. At the same time, the report stresses that much of the causation and aetiology of CFS is as yet little known or understood.

15. Immediate steps that commissioners of services can undertake are:

- identify which specialist units in their area are equipped to undertake the treatment of patients with established CFS
- review with those units their knowledge and understanding of the issues raised in the joint working groups report
- draw the findings in the report to the attention of general practitioners; it may be helpful to involve the MAAG in this process.

16. The above course of action has no resource consequences. More effective management of CFS, particularly at the primary care preventive level, should avoid wastage of resources.

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