INTRODUCTION

Chronic fatigue syndrome is a relative newcomer to the medical scene, although the condition it describes certainly is not (Wessely, 1994). In this review I shall be concerned with the epidemiology of CFS, and will therefore emphasise those studies which take a population or primary care perspective. Although there is now a rich literature on many other aspects of CFS, ranging from immunology (Tirelli et al., 1994) to neuroimaging (Cope & David, 1996) and neuropsychology (Moss-Morris et al., 1996), few studies are population based, and few reviewers have considered epidemiological issues. This paper is a revision of an earlier paper on the same subject (Wessely, 1995).

CHRONIC FATIGUE SYNDROME. HISTORY

Chronic fatigue syndromes are neither new nor homogeneous. Various fatigue syndromes have been described over the years (Wessely, 1994), but the origins of modern CFS probably lie with the illness known to the Victorians as neurasthenia. This dominated the medical scene at the of the century (Shorter, 1992). It was largely superseded by the new psychiatric diagnoses, such as anxiety and depression, but traces of it survive in such conditions such as chronic brucellosis, reactive hypoglycaemia, chronic candidiasis and environmental hypersensitivity disorders. Neurasthenia itself remains a popular diagnosis in China, South East Asia and Eastern Europe.

One similarity between Victorian neurasthenia in its original formulation and CFS is the extent to which both caught the public imagination. When the Centre for Disease Control published its latest case definition (Fukuda et al., 1994) over 250,000 reprint requests were received. Others similarities can be found in the nature of the symptoms and profile of the typical sufferer, and the claims made concerning aetiology and treatment (Wessely, 1994; Abbey & Garfinkel, 1991). In particular, the frequent claims made by contemporaries for an infective or post infective origin to neurasthenia provide another strand linking past and present. It was the re-discovery of post infective fatigue that played an important role in the emergence of CFS, reflected in the prominence of labels such as chronic mononucleosis, post viral fatigue syndrome and others.

Another of the many origins of CFS can be found in the series of ill defined epidemics reported largely between 1930 and 1960 (Wessely, 1994; Aronowitz, 1992). These have been labelled according to either the particular location of well publicised outbreaks (Royal Free Disease, Iceland Disease), or by their resemblance to neurological conditions (epidemic neuromyasthenia, myalgic encephalomyelitis). These epidemics pose many problems in their own right, partly because most have not been investigated with modern rigour, and such evidence as is available suggests considerable heterogeneity (Levine et al., 1992; Briggs & Levine, 1994). Whereas many historical outbreaks were of a contagious, paralytic illness with neurological (or quasi neurological) signs, depending upon whether the contagion is viewed as infective (Staff et al., 1955) or emotional (McEvedy & Beard, 1970), and of good prognosis — CFS in current medical practice is sporadic, non contagious, fatiguing, without neurological signs, and of poor prognosis.
THE LANGUAGE OF CHRONIC FATIGUE

What exactly is chronic fatigue? Defining chronic is easy — the current consensus is that fatigue can be considered as chronic after six months of illness. There is as yet no particular logic for this division, but it is one of the few non controversial areas in this subject.

What about fatigue? In neurophysiological terms fatigue is the failure to sustain force or power output and can be objectively measured. In neuropsychology fatigue can refer to time related decrements in the ability to perform mental tasks, and can also be measured. Fatigue is also a subjective sensation, experienced by the patient, inaccessible to objective measurement, which can only be appreciated «second hand» (MacDougall, 1899; Muscio, 1921). Patients use a variety of terms to describe this elusive but unpleasant feeling, such as tiredness, weariness and exhaustion, as well as fatigue and weakness (David et al., 1988; Wessely & Powell, 1989). Such subjective fatigue is largely unrelated to «objective» measures of muscle fatigue and endurance, and overlaps with pain. It now seems clear that fatigue in CFS is not related to muscle fatigability, and is hence not associated with any objective measures of neuromuscular dysfunction. Likewise, there is little relationship between symptoms of mental fatigue and neuropsychological quantitative investigations (Wearden & Appleby, 1996). The core complaint of fatigue in CFS remains a private, subjective experience. Those seeking a definitive fatigue test, free from the influence of such ill defined variables as mood, personality, motivation and situation have long experienced frustration (Muscio, 1921).

The importance of the linguistic definitions can be seen in the differing prevalence of fatigue related symptoms. Tiredness is up to ten times commoner than weakness and twice as common as exhaustion (Tibblin et al., 1990; Lewis & Wessely, 1992). The difficulties of language are also illustrated by the finding that of the 16 adjectives used by psychiatrists to signify sadness, six were applied by patients to states of fatigue (Pinard & Tetreault, 1974). Even small differences in terminology can result in considerable differences in research findings.

DEFINITIONS OF CFS

In 1988 David et al. (1988) argued that the lack of information on the prevalence, nature and aetiology of CFS could be traced to the lack of epidemiological data and neglect of epidemiological principles, in much of the published studies. Annual prevalence estimates then varied from 3 to 2800 per 100,000. Extraordinary variation in diagnostic practice remains. The diagnosis is made in anything between 1 in 60 to 1 in 10,000 Scottish general practice patients (Clements, 1991), whilst only one third of primary care physicians in St Louis report seeing any cases at all (Alisky et al., 1991).

The biggest advance has been the introduction of two operational case definitions which have become widely used. One started with the efforts of American infectious disease and immunology specialists (Holmes et al., 1988), and has been refined on two occasions (Schluederberg et al., 1992; Fukuda et al., 1994). A second comes from a British consensus conference (Sharpe et al., 1991). These definitions are listed in table I. They are a number of similarities, such as the requirement for substantial functional impairment in addition to the complaint of fatigue (although all are vague on how this should be measured). Differences are also apparent. For example, the American criteria attach particular significance to certain somatic symptoms such as sore throats, painful muscles and lymph nodes, and, although the requirement for multiple symptoms has been modified in the latest revision, four somatic symptoms chosen from a list of eight are still required. The choice of symptoms reflects one school of thought that holds that an infective and/or immune process underlies CFS. In contrast, the British definition does not emphasize somatic symptoms, instead insisting on both physical and mental fatigue and fatigability. It is too early to state what are the implications of these differences, but all are purely operational criteria for clinical research, and none have any particular validity. That there are any pathognomic symptoms that mandate a diagnosis of CFS seems highly unlikely (Wessely et al., 1996; Chester, 1997).

EPIDEMIOLOGY OF CHRONIC FATIGUE

Before considering the epidemiology of CFS, it is first necessary to consider what is known about the chief symptom, chronic fatigue. There are numerous studies of the prevalence of fatigue, all of which conclude that it is one of the commonest symptoms en-
Table I. - Case definitions for Chronic Fatigue Syndrome.

<table>
<thead>
<tr>
<th></th>
<th>CDC -1988</th>
<th>CDC-1994</th>
<th>Australian</th>
<th>UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum duration (months)</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Functional impairment</td>
<td>50% decrease in activity</td>
<td>Substantial</td>
<td>Substantial</td>
<td>Disabling</td>
</tr>
<tr>
<td>Cognitive or neuropsychiatric symptoms</td>
<td>May be present</td>
<td>May be present</td>
<td>Required</td>
<td>Mental fatigue required</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>6 or 8 required</td>
<td>4 required</td>
<td>not specified</td>
<td>not specified</td>
</tr>
<tr>
<td>New onset</td>
<td>required</td>
<td>Clinically important</td>
<td>Known physical causes</td>
<td>Known physical causes</td>
</tr>
<tr>
<td>Medical exclusions</td>
<td>Extensive list of known physical causes</td>
<td>melancholic depression, substance abuse, bipolar disorders, psychosis, eating disorder</td>
<td>Psychosis, bipolar, substance abuse, eating disorder</td>
<td>Psychosis, bipolar, eating disorder, organic brain disease</td>
</tr>
<tr>
<td>Psychiatric exclusions</td>
<td>Psychosis, bipolar disorder, substance abuse,</td>
<td>melancholic depression, substance abuse, bipolar disorders, psychosis, eating disorder</td>
<td>Psychosis, bipolar, substance abuse, eating disorder</td>
<td>Psychosis, bipolar, eating disorder, organic brain disease</td>
</tr>
</tbody>
</table>

countered in the community (Lewis & Wessely, 1992). Typical findings are from a British community survey in which 38% of the sample reported substantial fatigue, which had been present for over six months in 18% (Cox et al., 1987). In Germany 26.2% of a population survey in Mannheim complained of «states of fatigue and exhaustion» over a seven day period (Schepank, 1987). Similar figures are encountered in other Western countries (Lewis & Wessely, 1992). Even in a working population, 11.5% of office staff reported six months or more of fatigue (Shefer et al., 1997).

Most of these fatigued people neither consider themselves ill, nor consult a doctor (Zola, 1966; Morrell & Wale, 1976). Many regard fatigue as «the norm», or an inevitable consequence of broken nights, overwork or stress (Popay, 1992). Despite that, fatigue remains a common symptom encountered in both primary and secondary care. A point prevalence of 21% for fatigue of six months duration, associated with other somatic symptoms such as sore throat, myalgia and headache, was recorded in an American primary care survey (Buchwald et al., 1987b). 32% of those attending an Israeli general practice reported at least one asthenic symptom (Shahar & Lederer, 1990). Slightly lower prevalence are reported in British primary care, where 10% will admit to chronic fatigue (David et al., 1990), and in Canada, where 14% of new attenders complained of fatigue, being the principal reason for consultation in 7% (Cathebras et al., 1992).

Relevant prevalence data can also be obtained from studies using the ICD-10 criteria for neurasthenia, which has considerable overlap with CFS — 97% of those attending a multidisciplinary CFS clinic in Wales also fulfilled criteria for neurasthenia (Farmer et al., 1995). In the Zurich longitudinal survey Merikangas & Angst reported prevalence of 6% for men and 10% for women (Merikangas & Angst, 1994). The recent multinational WHO study of mental disorder in primary care reported a prevalence of ICD-10 neurasthenia of 5.5% (Ormel et al., 1994). In the longitudinal study on the Swedish Island of Lundby the life time prevalence of fatigue syndrome (defined similarly to neurasthenia as excessive fatigue in the absence of clear cut features of anxiety or depression) was 33% for women and 21% for men (Hagnell et al., 1993).

Whatever the label, all agree that physical investigations are rarely helpful, except in certain groups such as the elderly (Lane et al., 1990; Valdini et al., 1989; Ridsdale et al., 1993).

Turning to medical outpatients, in an early study 9% of 1170 medical outpatients reported «tiredness, lassitude or exhaustion» as principal complaints (Ffrench, 1960). Nearly 30 years passed before another systematic enquiry. Looking at all symptoms experienced by hospital attenders, one third of those attending two American ambulatory medical clinics reported fatigue (Kroenke et al., 1990; Bates et al., 1993), making it the commonest overall symptom, and it was the main reason for presentation in 8% (Kroenke et al., 1990). Routine investigations failed to identify a cause for nearly all these subjects (Kroenke et al., 1990; Kroenke & Mangelsdorff, 1989).
EPIDEMIOLOGICAL DATA
ON THE PREVALENCE OF CFS

Chronic fatigue is thus common, but what about CFS? On the basis of laboratory request forms Ho-Yen estimated the prevalence in the West of Scotland as 51 per 100,000 (Ho-Yen, 1988). The first attempt at a population based study using an operational case definition came from Lloyd and colleagues in Australia (Lloyd et al., 1990). Cases were identified using general practitioners as key informants. A point prevalence of 37 per 100,000 was recorded. However, only 25% of those physicians approached agreed to participate. Ho-Yen and McNama (Ho-Yen, 1991) achieved a better response rate in their survey of Scottish general practitioners. They estimated a prevalence of 130 per 100,000, but recognition of CFS varied. Professional workers remained over-represented, although this could still reflect differences in labeling. CFS consumed considerable amounts of medical time. The Center for Disease Control and Prevention (CDC) attempted to estimate the prevalence of CFS based on surveillance of selected physician’s in four US cities (Anon, 1997). The observed prevalence of CFS were lower than the Australian figures — between 2 to 7 per 100,000. There was a female excess, and a high rate of psychiatric morbidity. All of these studies are examples of key informant/sentinel physician designs, and all suggest that CFS is not a common problem in primary care.

Recent studies with systematic case ascertainment report a different picture. Bates et al. (1993) surveyed an American Ambulatory care clinic. In keeping with the literature 27% of those attending a primary care clinic had substantial fatigue lasting more than six months and interfering with daily life. The point prevalence of CFS according to the various definitions was 0.3% (CDC-1988), 0.4% (UK) and 1.0% (Australian) respectively. In a study of a Health Maintenance Organisation in Seattle Buchwald and colleagues report a prevalence between 0.07 to 0.3%, depending on the assumptions made (Buchwald et al., 1995). Similar findings will emerge from a random household survey carried out in San Francisco (Steele et al., in press). 1.6 % of employees in a large office complex in California reported previous diagnoses of CFS (Shefer et al., 1997), whilst 1% of a sample of US nurses satisfied criteria for CFS (Jason et al., submitted for publication).

In a primary care study from the United Kingdom, CFS had prevalence ranging from 0.8% (CDC 1988) to 1.8% (CDC 1994)(Wessely et al., in press). Many of these were co morbid with common psychiatric disorders, but even when these had been excluded the prevalence of CFS was 0.5% (CDC 1994) or 0.7% (Oxford criteria). In Scotland the prevalence was 0.6%, although the sample size was relatively small (Lawrie & Pelosi, 1995). The Scottish researchers then performed a follow up one year later (Lawrie et al., 1997). This time the prevalence of CFS was 0.7%, but they were also able to make the first estimate of the incidence of CFS, which was 370 per 100,000 (once again, however, with rather wide confidence limits).

What can we conclude from these results. First, that estimates of prevalence based on selected samples (specialist centres or key informants) both under estimate prevalence, and, as we will see later, emphasise features of the disorder that turn out to be atypical. Nearly all those who fulfilled operational criteria for CFS were not labelled as such by either themselves or their general practitioners, and thus would not be identified in a key informant survey, or a tertiary setting (Wessely et al., in press). Others might be reluctant, or unable, to access health care (Jason et al., 1995). Among the vast numbers of subjects with excessive fatigue, only 1% believed themselves to be suffering from CFS (Pawlikowska et al., 1994). This emphasises just how few of those who could be classified as CFS are labelled as such, or seek specialist help, and highlights the powerful role of selection bias in previous studies, which are almost all based on tertiary care samples of patients who have frequently made their own diagnosis before seeking specialist help, and are almost certainly an atypical and unrepresentative sample of CFS cases (Richman et al., 1994).

Second, UK primary care studies seem to give the higher estimates of prevalence. This may either reflect the different set of instruments used, or alternatively the influence of illness behaviour. At present most investigators use a combination of various instruments measuring different aspects of CFS (fatigue, somatic symptoms, functional impairment and so on) rather than a single validated measure, which may account for some of the variations. American researchers are starting to make progress in this area, but much remains to be done (Jason et al., 1997).

THE ROLE OF PSYCHOLOGICAL DISORDER

Fatigue and psychological disorder go together.
Table II. - Current psychiatric disorder in CFS compared to medical controls.

<table>
<thead>
<tr>
<th>Author</th>
<th>Control Group</th>
<th>% Psychiatric disorder: CFS</th>
<th>% Psychiatric disorder: controls</th>
<th>Relative risk of psychiatric disorder in CFS compared to controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Wessely &amp; Powell, 1989)</td>
<td>neuromuscular</td>
<td>72%</td>
<td>36%</td>
<td>2.0</td>
</tr>
<tr>
<td>(Katon et al., 1991)</td>
<td>rheumatoid arthritis</td>
<td>45%</td>
<td>6%</td>
<td>7.5</td>
</tr>
<tr>
<td>(Wood et al., 1991)</td>
<td>myopathy</td>
<td>41%</td>
<td>12.5%</td>
<td>3.3</td>
</tr>
<tr>
<td>(Pepper et al., 1993)</td>
<td>multiple sclerosis</td>
<td>23%</td>
<td>8%</td>
<td>2.9</td>
</tr>
<tr>
<td>(Fischler et al., 1997)</td>
<td>ENT/ dermatology</td>
<td>77%</td>
<td>50%</td>
<td>3.4</td>
</tr>
<tr>
<td>(Lynch, 1997)</td>
<td>diabetes</td>
<td>81%</td>
<td>28%</td>
<td>2.9</td>
</tr>
<tr>
<td>(Johnson et al., 1996ba; Johnson et al., 1996a)</td>
<td>multiple sclerosis</td>
<td>45%</td>
<td>16%</td>
<td>2.8</td>
</tr>
</tbody>
</table>

As an isolated symptom fatigue remains associated with affective disorder, frequently preceding the development of major depressive disorder in primary care (Wilson et al., 1983). Fatigue alone was associated with an adjusted odds ratio of 2.6 (women) and 6.8 (men) for subsequent major depressive disorder one year later (Dryman & Eaton, 1991). Depression and anxiety are the most robust associations of fatigue in primary care (Kroenke et al., 1988). The presenting symptoms of sleep disturbance, fatigue, multiple complaints and musculoskeletal symptoms, all which are common in CFS, were the best discriminators between depressed and non depressed primary care subjects (Gerber et al., 1992). 72% of those with excessive fatigue seen in primary care were assigned a psychiatric diagnosis according to ICD-9 (McDonald et al., 1993).

Numerous studies have now been published concerning the role of psychiatric disorder in CFS, of which 11 use direct interviews (see (David, 1991; Clark & Katon, 1994)). A variety of instruments and operational criteria have been used, but the results are surprisingly consistent. Approximately half of those seen in specialist care with a diagnosis of one or other form of CFS fulfil criteria for affective disorder, even with fatigue removed from the criteria for mood disorder. The majority of studies find that a further quarter fulfil criteria for other psychiatric disorders, chief amongst which are anxiety and somatisation disorders. Nearly all also agree that between one quarter to one third do not fulfil any criteria. Conversion disorder, a preoccupation of the media, is rare. The figures for the comorbidity of neurasthenia and psychiatric disorders are also congruent with these findings — in the multinational WHO study of mental disorder in primary care (Ormel et al., 1994) ICD-10 neurasthenia showed 71% psychiatric comorbidity.

These studies have been discussed at length elsewhere (David, 1991; Clark & Katon, 1994). Four explanations have been suggested. The first is that the observed psychological distress is a reaction to physical illness. This is the least likely explanation. It assumes that a discrete and or unique physical pathology and symptoms can be identified — this has yet to occur. Furthermore, those studies that compare the rates of psychiatric disorder in CFS with those of medical controls find that the risk of psychiatric disorder is elevated in the CFS cases (table II).

The second explanation is of misdiagnosis of psychiatric illness. The third suggests a common origin to both CFS and psychiatric disorder, the result of a common neurobiological process (Demitrack & Greden, 1991). There is a rapidly increasing literature on the results of neuropsychological and neuroimaging investigations in CFS which lie beyond the scope of this review, but lend support to this position. A recent series of neurobiological studies have suggested disturbances of the hypothalamic pituitary axis and of neurotransmitter pathways that control hypothalamic function in CFS — intriguingly although disturbances in these pathways are implicated in the pathogenesis of major depressive disorder as well, the direction of change observed in CFS is not identical to that found in CFS (Demitrack & Greden, 1991; Cleare et al., 1995; Sharpe et al., in press)

The final explanation of the association between CFS and psychological morbidity is that it is an inevitable artefact of the overlap between the current operational concepts of both CFS and psychiatric disorder (vide infra). These explanatory models are not mutually exclusive.
One current unresolved issue is raising the question of whether or not psychological disorders, past or present, should be excluded from the diagnosis of CFS, as they are in the current concepts of neurasthenia. Excluding on the basis of past psychiatric disorder has considerable drawbacks. In the CDC study (Gunn et al., 1993) 45% of those who would otherwise have fulfilled the CFS criteria were excluded because of prior psychiatric disorder, yet in other respects resembled the full CFS cases (and no doubt believed they too had CFS). It assumes that previous psychiatric disorder excludes a diagnosis of CFS, although some (but not all) tertiary care studies suggest that it may be a risk factor. Nor does this strategy give rise to a «pure» CFS sample, free from the taint of psychiatric disorder. New cases of psychiatric disorder can arise without a previous history, and still present as CFS.

**GENDER**

Nearly all published studies report that women are over-represented in specialist samples of CFS. A comparison of male and female CFS patients in a specialist centre revealed few clinical differences (Buchwald et al., 1994). Most authors suggest gender differences observed in clinical samples could be an artefact of illness behaviour and referral. However, it should be noted that even in community studies women are more likely to report fatigue and chronic fatigue than men — the relative risk of fatigue in women compared to men in one community study was 1.3 (Pawlikowska et al., 1994). In primary care the relative risk for women varies between 1.3 and 1.7 (David et al., 1990; Cathebras et al., 1992; Fuhrer & Wessely, 1995).

There is an obvious similarity between these findings and those reported for gender differences in depression — for example, in the National Comorbidity Survey women were approximately 1.7 times as likely as men to report a lifetime history of depression (Kessler et al., 1994). Affective disorder is well known as one of the strongest associations of fatigue. However, although controlling for depression removed the gender difference in fatigue in one community study (Chen, 1986), this was not found in two others (Cox et al., 1987; Pawlikowska et al., 1994) studies. Pawlikowska and colleagues noted that as various restriction criteria of increasing stringency were applied (such as duration, percentage of time tired, presence of myalgia), the ratio of female to male cases increased (Pawlikowska et al., 1994) — a household study in Michigan reported similar findings (Fukuda et al., 1997).

**INFECTION**

Many patients encountered in specialist care, including infectious disease clinics (Petersen et al., 1991), immunology clinics (Hinds & McCluskey, 1993), neurological centres (Behan & Behan, 1988; Wessely & Powell, 1989) or fibromyalgia clinics (Buchwald et al., 1987a) report that their illness followed an apparent infective episode, with the curious exception of Japan, where most CFS patients do not recall such an association (Minowa & Jiamo, 1996).

However, there are a number of methodological reasons why such associations should not be accepted uncritically (Wessely, 1991; Klonoff, 1992). Viral infection is extremely common in the community — up to one third of the population will reply positively to a question asking if they have experienced a viral infection in the last month (Cox et al., 1987). Chance alone may be responsible for the apparent association with an infective onset. The techniques used to detect previous exposure to viral infection in patients with long illness duration are prone to error. Search after meaning and recall bias are also important, since there are psychological and social reasons why people may attribute their fatigue syndrome to a virus, in contrast to any possible role of psychosocial factors.

It is thus not surprising that the initial enthusiasm for the role of Epstein-Barr virus in the United States has now subsided (Straus, 1988). Claims have also been made for another herpes virus, Human herpes virus -6 (HHV-6). HHV-6 infection is ubiquitous, rendering interpretation of serological studies difficult, but a recent review concluded that whereas it was an unlikely aetiological candidate, secondary reactivation by some other mechanism or stress might contribute to symptoms (Hay & Jenkins, 1994).

In Great Britain early studies pointed to a role for the enterovirus family. The tests on which these claims were based are now known to be faulty. Further excitement resulted from the introduction of newer tests, such as the polymerase chain reaction (Gow et al., 1991; Clements et al., 1995), but later studies again show equal levels of exposure in cases and controls for these probes as well (Miller...
et al., 1991; Gow et al., 1994; Swanink et al., 1994; 1995; Straus, 1996; Lindh et al., 1996). At present there is no compelling evidence for enteroviral involvement in CFS. Finally, in a controlled prospective study of the outcome of over one thousand symptomatic infective episodes seen in British primary care we have been unable to demonstrate any link between infection and subsequent chronic fatigue and chronic fatigue syndrome (Wessely et al., 1995).

We have thus learnt to show more caution about over enthusiastic espousal of links between specific infection and CFS. Infective triggers for CFS do remain on the agenda, although the wealth of evidence reporting cases of CFS arising after a number of agents, viral, bacterial and even protozoal, suggests that the condition is more likely to represent a non specific response to a number of infective (and non infective) agents, than solely attributable to any single agent (Swartz, 1988; Fekety, 1994). Dividing cases into that were apparently triggered by an infection and those that were not does not appear to identify a distinct subgroup (Wood, 1941; Buchwald et al., 1996b), although dividing subjects into those with acute or chronic onsets may have promise (De Luca et al., 1997; Mawle et al., 1997).

At present, epidemiological data does not confirm a link between CFS and the common infective agents encountered in everyday life. However, a population perspective cannot exclude a rare reaction to a common infection, or alternatively, a common reaction to an unusual agent. Sound epidemiological data has been presented for only a few agents, principally the Epstein Barr virus, which having been discounted by researchers is now undergoing something of a renaissance in CFS studies. A prospective longitudinal primary care study of the outcome of EBV infection demonstrates that EBV and non-EBV glandular fever are associated with a post infectious fatigue syndrome distinct from, and commoner than, depression (White et al., 1995). Brief reports from Australia suggest that a similar conclusion may be reached in studies of the outcome of Q fever (Marmion et al., 1996).

IMMUNE DYSFUNCTION

Great attention has been given to the role of possible immune dysfunction in CFS, either as the primary cause of the syndrome, or alternatively as a consequence of some other process, such as chronic infection. There is indeed evidence of some laboratory abnormalities, with the promising findings emerging from studies of T-cell subsets and natural killer cells (Klimas et al., 1990), although even in these areas there is no unanimity of findings (Mawle et al., 1997; Natelson et al., in press). The observed findings are also relatively non specific, and do not appear to be related to outcome (Buchwald & Komaroff, 1991; Peakman et al., 1997). The role of potential confounders such as inactivity and psychiatric morbidity also remains unclear (Strober, 1994). No reported immunological abnormalities can, as yet, be placed in an epidemiological context. There is a pressing need for a systematic review of the findings to date.

SELECTION BIAS

There is general agreement that CFS as observed in specialist centres has certain characteristics. For example, study after study reports that sufferers are more likely to be females, come from higher socio-economic groups, and indeed show a particular over representation of certain professions, such as teachers or nursing. Of the 3,000 individuals who phone the Center for Disease Control CFS Information Line every month a quarter are medical or para-medical (Gunn, 1993). The occasional attempt is made to explain this finding in terms of viral exposure (both in childhood and at work), and overwork. Such explanations (reminiscent of those advanced to account for the same apparent excess of middle class professionals in the ranks of neurasthenia sufferers (Sicherman, 1977; Wessely, 1994)) are unconvincing, with the possible exception of EBV virus, since lower socio-economic status is associated with an increased risk of primary EBV infection in childhood (Sumaya & Ench, 1985). Other explanations include access to health care, and differential labelling by both sufferer and doctor. In contrast to the pattern observed in specialist samples of CFS, there is no evidence for any excess of higher socio-economic status for fatigue, chronic fatigue or chronic fatigue syndrome observed in the community or primary care (Cox et al., 1987; Wessely et al., in press; Fukuda et al., 1997; Shefer et al., 1997).

Likewise, strong physical attributions and intense disease conviction are the norm. In contrast, ethnic minorities are rarely encountered. However, are any
of these actually characteristics of the condition, or do they reflect the well known «clinician’s illusion». (Cohen & Cohen, 1984). We have compared cases of CFS identified recruited during the conduct of a systematic survey in primary care with those attending our specialist clinic. The results suggest that both the apparent excess of higher social classes, and the association with strong physical convictions, are more the product of selection bias rather than intrinsic to the condition (Euba et al., 1996).

Another feature of CFS as seen in specialist practice is the close association with psychological disorders (vide supra). How much does this represent referral bias and the influence of psychological morbidity on illness behaviour? An analogous situation is that of irritable bowel syndrome (IBS). In cases of IBS seen in gastroenterological practice there is a consistent relationship with psychological disorders such as depression and anxiety. This relationship is far weaker in community cases of IBS, suggesting that the links between IBS and psychological morbidity in clinical practice are a product of illness behaviour and referral patterns (Whitehead et al., 1988; Smith et al., 1990).

This has not been demonstrated in CFS. Subjects fulfilling criteria for CFS seen in primary, secondary and tertiary care differ in many ways, but not in the overall prevalence of psychological disorder (Cope et al., 1996; Wessely et al., 1996). Even in primary care introducing the more restrictive criteria for CFS strengthens, and not weakens, this association, as in tertiary care (Katon & Russo, 1992; Wessely et al., 1996).

The overlap between psychological disorder and CFS seems to persist in which ever setting one looks. This is far from surprising. One of the most robust findings in psychiatric epidemiology is that the greater the number of somatic symptoms, the greater the risk of psychiatric disorder (Goldberg & Huxley, 1992). Similarly, the greater the number of pain symptoms, the greater the risk of depression (Dworkin et al., 1990). One of the salient features of CFS patients is that they experience not only fatigue, but a variety of other somatic symptoms as well (Lane et al., 1991). Whereas controlled studies usually find that CFS patients lie midway between normal and psychiatric controls on measures of standard psychological distress, they are usually the group with the most somatic symptoms (Wessely & Powell, 1989; Katon et al., 1991; Lane et al., 1991; Blackley et al., 1991). Current concepts of CFS emphasise its polysymptomatic nature (Holmes et al., 1988; Fukuda et al., 1994) — those fulfilling the criteria have more functional somatic symptoms than fatigued patients who do not make the criteria.

Katon & Russo (1992) concluded that «the patients with the highest numbers of medically unexplained symptoms had extraordinarily high rates of current and lifetime psychiatric disorders». In a community study (Pawlikowska et al., 1994) we noted a close and linear relationship between fatigue and psychological disorder as measured by questionnaire (table I). In the subsequent primary care study we found a similar close relationship between the risk of psychiatric disorder, measured by questionnaire or interview, and the number of somatic symptoms, either all symptoms, or just those endorsed by the CDC (Wessely et al., 1996). The latest definition from the CDC (Fukuda et al., 1994), which continues to emphasise the requirement for multiple and specific somatic symptoms (albeit reduced from earlier definitions) thus reflects an uneasy compromise between on the one hand British and Australian researchers, who have argued that it would as logical to have a maximum, rather than minimum, number of non fatigued symptoms, and on the other some American views of CFS as a specific disease entity resulting from an as yet undiscovered pathological process.

Studies showing that fatigue and exhaustion are one of the cardinal features of affective disorder are too numerous to mention. They are also core features of panic and somatisation disorders. Other physical symptoms reported in major depression, agoraphobia, somatisation and panic disorders also overlap with those reported in CFS. Hence the association between emotional morbidity and chronic fatigue syndrome is inevitable given the similarities of the criteria used to identify them. It should not, however, be assumed to be causal. As Kendell has written 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» (Kendell, 1991). The same criticisms and limitations identified for CFS apply in equal measure to the operational definitions currently used for common psychological disorders. Links with operationally defined psychiatric disorder should also not obscure the considerable variation and heterogeneity within psychiatric diagnostic categories themselves.

At present, therefore, CFS lies in an ambiguous space between medical and psychiatric classifications. For some subjects, existing psychiatric classifications appear perfectly adequate. If we follow Occam’s Razor we do not need to invent more categories than are necessary, even if encouraged to do
so by social pressures. For others, links to psychiatric disorders exist, in the sense of overlap, but current definitions appear unsatisfactory. Just as fatigue lies in a dimensional space between depression and anxiety (Goldberg et al., 1987), chronic fatigue syndrome/neurasthenia likewise has links with both depression and anxiety, but is synonymous with neither, and attempts to shoe horn all cases of CFS into one or the other category seem doomed to fail.

CFS AND THE SPECTRUM OF FATIGUE

So far it has been assumed that fatigue is something one either has, or doesn’t have. This dichotomous approach is an essential pre-requisite for determining conventional epidemiological indices of incidence and prevalence. It is also the basis of medical practice — doctors treat cases. However, is this accurate? Is there a qualitative difference between «normal» fatigue and «abnormal» fatigue?

There is considerable evidence to support a dimensional, rather than a categorical, view of fatigue. To quote the late Geoffrey Rose: «the real question in population studies is not ‘Has he got it?’, but ‘How much of it has he got?’» (Rose & Barker, 1978). Goldberg & Huxley (1992) wrote: «it would be tedious to enumerate the surveys which have shown that symptoms are continuously distributed in the population: rather than attempt to do this, we will observe that we are unaware of a single survey that shows anything else». The same could be argued for fatigue. Several studies from primary care or the community now suggest that fatigue and related asthenic symptoms are indeed continuously distributed (David et al., 1990; Lewis & Wessely, 1992; Pawlikowska et al., 1994).

The precise point at which normal fatigue shades into the disabling experience of CFS is both unclear and arbitrary. Back in 1908 Wells advocated «shifting the viewpoint from the measurement of discrete states of fatigue to continuous determinants of susceptibility» (Wells, 1908). In the current political climate surrounding CFS it is, however, important to note that this dimensional view of fatigue no more invalidates the illness status of chronic fatigue syndrome than the dimensional distribution of hypertension invalidates the risks associated with high blood pressure.

The present evidence suggests that fatigue is a dimensional, not categorical variable. As the experience of fatigue increases in severity, a person is more likely to present to a doctor with the complaint, and hence view him or herself as ill. Increasing severity of fatigue is also associated with increased functional impairment, a greater number of other somatic symptoms and higher psychological distress. Only a minority of those with chronic fatigue fulfil criteria for CFS (Bates et al., 1993; Katon et al., 1991; McDonald et al., 1993; Manu et al., 1988a) — but these may reflect the arbitrary end of a spectrum of severity, just as fibromyalgia has been argued to represent the severe end of a spectrum of muscle pain, tenderness and fatigue (Makela & Heliovaara, 1991; Croft et al., 1994). No doubt new discrete causes of fatigue and myalgia syndromes remain to be uncovered, just as hypertension is occasionally caused by renal artery stenosis or phaeochromocytoma, but it is the role of population based studies to place these in their epidemiological context.

FUNCTIONAL IMPAIRMENT

It has already been noted that patients seen in specialist settings, or those recruited from self help groups, may be untypical in terms of social class. They have also been ill a long time. The mean duration of illness was five years in patients referred to a either a neurological hospital (Wessely & Powell, 1989) or an immunology clinic (Hinds & McCluskey, 1993) and 13 years in those attending a special fatigue clinic (Manu et al., 1988b). CFS cases recruited from these settings (from where nearly all aetiological studies have originated) have considerable morbidity, enshrined in the current definitions of CFS all of which insist on functional impairment.

Functional impairment in CFS is even more profound (Lloyd & Pender, 1992; Buchwald et al., 1996a; Wessely et al., in press). This is partly artefactual, because functional impairment is a requirement of all the current definitions, but impairment remained profound if this requirement was removed from the operational criteria employed. The greater the fatigue, the greater the impairment (Buchwald et al., 1996a). We found a close link between functional impairment and psychological morbidity (Wessely et al., in press). The WHO study also found an association between psychiatric comorbidity and functional disability for neurasthenia (Or-
mel et al., 1994). In contrast another study found that functional impairment was greater in CFS than in depressed controls, whilst there was no relationship between mental health and other CFS symptoms (Komaroff et al., 1996).

Even in primary care chronic fatigue has a substantial impact. Of the symptoms studied in a single inner London general practice fatigue had the strongest association with functional impairment. Of those who admitted tiredness, 26% said it had forced them to restrict their normal activities, and 28% reported needing to lie down in response to the symptom (Morrell & Wale, 1976). Still in primary care Nelson and colleagues observed that «about one-third of sufferers indicate that it seriously erodes their overall enjoyment of life and renders them unable to carry out their usual role activities»(Nelson et al., 1987). 28% of patients with chronic fatigue had been completely bedridden at some stage (Buchwald et al., 1987b). In our primary care study chronic fatigue subjects had worse mental health, more bodily pain, worse perception of their health and greater physical impairment than non-fatigued controls. For comparison the data from the Medical Outcomes Study (Wells et al., 1989) showed higher scores (indicating better functioning) for subjects with diabetes, hypertension and arthritis. Only angina and advanced coronary artery disease scored less. Mean role functioning for chronic fatigue was substantially lower than that for hypertension or diabetes, and again only advanced coronary artery disease scored less.

CONFOUNDING

Such severe functional impairment introduces the subject of confounding. Lack of physical activity has profound effects on muscle function and chemistry as well cardiac function, and may also affect both immune and psychological status. Particularly relevant is that lack of activity is itself a risk factor for fatigue (Chen, 1986; Valdini et al., 1987; Ross & Hayes, 1988), which may set up a vicious circle of inactivity and impairment (see (Klug et al., 1989; Wessely & Sharpe, 1995). Studies of CFS have reported abnormalities in many aspects of neuromuscular, cardiac, immunological and psychological functioning, yet the possible confounding role of inactivity is not always addressed.

PROGNOSIS

The prognosis of chronic fatigue in tertiary care is gloomy. In the Mayo clinic 235 patients with a diagnosis of chronic nervous exhaustion were followed up approximately 6 years later (Macy & Allen, 1934). Most remained symptomatic, although precise figures are not given. 173 cases of neurocirculatory asthenia seen by a single cardiologist were followed up for an average of 20 years (Wheeler et al., 1950). Only 11% were asymptomatic, whilst 38% were mildly, and 15% severely, disabled.

Little has changed with the arrival of CFS. Behan & Behan (1988) write that «most cases do not improve, give up their work and become permanent invalids». In a systematic review of prognosis we found that less than 10% of adults attending specialist settings made a complete recovery in the short or medium term (Joyce et al., 1997). The Oxford and Sydney groups both reported that the strongest association of failure to recover was strength of the belief in a solely physical cause to symptoms, and also the presence of psychiatric disorder (Sharpe et al., 1992; Wilson et al., 1994). Several publications have outlined models linking illness beliefs, such as the conviction that symptoms are the sole result of a persistent viral infection, with the perpetuation of disability (see Wessely & Sharpe, 1995; Abbey, 1993 for reviews).

If that is so, then one might predict that the prognosis of CF and CFS in primary care should be better than that found in specialist care, since some of the factors associated with poor prognosis are less prominent in the former settings (Euba et al., 1996). Lawrie and colleagues in a one year study did indeed report a better prognosis (Lawrie et al., 1997) in primary care. However, although better than in tertiary centres, the prognosis for chronic fatigue even in the population appears to be guarded. Instead we suspect that many individuals periodically satisfy criteria for CF and/or CFS, but this will fluctuate over time, due the interaction between environmental factors and an underlying, presumably constitutional and/or genetic predisposition.

OTHER FATIGUE SYNDROMES

No mention has been made of a variety of other syndromes, common in medical practice, in which fatigue is a prominent symptom. These include fibro-
myalgia, irritable bowel syndrome, effort syndrome, hyperventilation syndrome, and the various so-called allergy or chemical sensitivity syndromes. In all of these not only is fatigue prominent, but so are many of the other somatic symptoms found in CFS. Studies that have looked for it report overlaps between CFS and irritable bowel (Gomborone et al., 1994), multiple chemical sensitivity (Buchwald & Garrity, 1994), fibromyalgia (Buchwald, 1996) and premenstrual syndrome (Dobbins et al., 1995). We suspect that considerable overlaps exists between all the various syndromes based on medically unexplained symptoms (Nimmuan et al., submitted for publication). The choice of diagnosis for such patients may be an arbitrary process, influenced by factors such as the patients’ presenting complaint and local referral practices.

CONCLUSIONS

Chronic fatigue is a common somatic symptom, frequently encountered at all levels of the health care system. Like most things, it is dimensionally distributed, with on the one hand it presenting as an exacerbation of a feeling we all experience as part of normality, whilst at the other extreme it is associated with distress and disability that have few equals in medical practice. At that extreme lie those who fulfill criteria for what we currently call chronic fatigue syndrome, but the nosological status of that categorical diagnosis remains unclear.

No single aetiologic cause exists for CFS — instead, it is almost certainly the last stage of a multifactorial process. That last stage seems to be best understood as a disorder of the perception of effort — both motor effort and cognitive effort (Fry & Martin, 1996; Lawrie et al., 1997a). Predisposing factors remain largely unstudied, but personality, genetics and previous psychological disorder may all play a role. Somatic insults, such as severe or unusual infections, seem to have an important role as precipitants. Perpetuating factors may include physiological factors, such as inactivity and sleep disorder, psychological factors such as mood and illness beliefs, and somatic factors such as disturbances of the neuroendocrine axes.

The rise to prominence in the Anglophone world of the label of CFS and its local variants has led to a corresponding increase in professional recognition and research activity. Nevertheless, it remains important to distinguish between the epidemiological associations of an operationally defined condition (CFS), and those of an illness belief (CFIDS, ME or other variants). This two are not the same thing, and need to be carefully distinguished.

The final question of interest is the relationship between CFS and comorbid CFS. It has already been suggested that CFS is accompanied by high rates of comorbid psychiatric disorder, and that psychiatric disorder is associated with functional impairment. However, no study has ever reported complete congruence between CFS and psychiatric disorder. Do the associations of CFS differ according to the presence or absence of comorbidity? A suggestion that this might be so comes from the important cohort study of the outcome of EBV and EBV-like infections already discussed (White et al., 1995). Acute social adversity was strongly associated with the development of depression after glandular fever. However, «pure» post-infectious fatigue syndrome (ie without comorbid depression) was not associated with life events (Bruce-Jones et al., 1994). The implication is that acute social adversity predicts comorbidity in fatigue syndrome (the commonest situation), but not fatigue syndrome per se.

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The epidemiology of chronic fatigue syndrome

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