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The Epidemiology of Chronic Fatigue Syndrome

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INTRODUCTION

After years of relative obscurity, the problems of patients with excessive fatigue that defies simple explanation are again in the news. These symptoms are now acquiring the label "chronic fatigue syndrome" (CFS). The subject of CFS is extraordinarily rich and complex. Recent reviews and chapters have considered the condition from the point of view of such diverse disciplines as anthropology, endocrinology, history, immunology, neurophysiology, neuropsychology, psychiatry, and virology. Progress has been made in many of these fields, although consensus remains elusive. This review concerns the epidemiology of CFS, and it will therefore emphasize studies that have taken a population or primary care perspective. Readers requiring detailed information on nonepidemiologic aspects of CFS are referred elsewhere (1, 2).

HISTORY OF CFS

Chronic fatigue syndromes are neither new nor homogeneous. Various fatigue syndromes have been described over the years (3), but the origins of modern CFS probably lie with the illness known to the Victorians as neurasthenia. This illness dominated the medical scene at the turn of the century (4). It was largely superseded by the new psychiatric diagnoses, such as anxiety and depression, but traces of it survive in such conditions as chronic brucellosis, reactive hypoglycemia, chronic candidiasis, and environmental hypersensitivity disorders. Neurasthenia itself remains a popular diagnosis in China, Southeast Asia, and Eastern Europe.

One similarity between Victorian neurasthenia in its original formulation and CFS is the extent to which both caught the public's imagination. Other similarities can be found in the nature of the symptoms, the profile of the typical sufferer, and the claims made concerning etiology and treatment (3, 5). In particular, the frequent claims made by contemporaries for an infective or postinfective origin of neurasthenia provide another strand linking past and present. It was the rediscovery of postinfective fatigue that played an important role in the emergence of CFS, reflected in the prominence of labels such as chronic mononucleosis, postviral fatigue syndrome, and the like.

Another of the many origins of CFS can be found in the series of ill-defined epidemics reported largely between 1930 and 1960 (3, 6). These epidemics have been labeled according to either the particular location of well-publicized outbreaks (Royal Free Disease, Iceland Disease) or their resemblance to neurologic conditions (epidemic neuromyasthenia, myalgic encephalomyelitis). These epidemics pose many questions in their own right, and are of undoubted historical relevance for the emergence of CFS. However, this paper will be restricted to the epidemiology of sporadic cases of CFS. With the occasional exception, epidemics are no longer common—most cases now appear sporadic. Most epidemic outbreaks have not been investigated with modern rigor, and such evidence as is available suggests considerable heterogeneity (7, 8). Whereas many historical outbreaks were of a contagious, paralytic illness with neurologic or quasi-neurologic signs (depending upon whether the contagion is viewed as infective (9) or emotional (10)) and of good prognosis, CFS in current medical practice is noncontagious, fatiguing, without neurologic signs, and of poor prognosis. Although in some countries such as the United Kingdom the term "myalgic encephalomyelitis" has been applied to both epidemic and sporadic manifestations, there is little epidemiologic evidence to suggest that similar processes are involved.

THE LANGUAGE OF CHRONIC FATIGUE

What exactly is chronic fatigue? Defining "chronic" is easy—the current consensus is that fatigue can be considered chronic after 6 months of illness. There is

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Abbreviations: CDC, Centers for Disease Control and Prevention; CFS, chronic fatigue syndrome; ICD-9 or -10, *International Classification of Diseases,* Ninth or Tenth Revision.

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as yet no particular logic for this division, but it is one of the few noncontroversial areas in this subject.

What about fatigue? In neurophysiologic terms, fatigue is the failure to sustain force or power output, and it can be objectively measured. In neuropsychology, fatigue can refer to time-related decrements in the ability to perform mental tasks, and it too can be measured. Fatigue is also a subjective sensation experienced by the patient, inaccessible to objective measurement, which can only be appreciated "secondhand" (11, 12). 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 (13, 14). Such subjective fatigue is largely unrelated to "objective" measures of muscle fatigue and endurance, and it overlaps with pain. It now seems clear that fatigue in CFS is not related to muscle fatigability. Similarly, although some studies from specialist centers report abnormalities in measures of neuropsychological function, the results, especially those from primary care samples, are inconsistent (15). The core complaint of fatigue in CFS remains a private, subjective experience.

The importance of the linguistic definitions can be seen in the differing prevalences of fatigue-related symptoms. Tiredness is up to 10 times more common than weakness and twice as common as exhaustion (16, 17). 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 (18). Even small differences in terminology can result in considerable differences in research findings.

This problem of definition and measurement has many implications. Most patients presenting with chronic fatigue lack any objective abnormality documenting their problem, let alone indicating its cause (vide infra). This absence of validating evidence poses problems for both patient and doctor. Persons seeking a definitive fatigue test free from the influence of such ill-defined variables as mood, personality, motivation, and situation have long experienced frustration (12). A modern neurobiologist noted the problems involved in distinguishing postviral fatigue from affective disorder and concluded, "One advance which would clarify this issue would be the ability to document weakness in patients objectively" (19, p. 810). This advance remains elusive.

DEFINITIONS OF CFS

The rise of CFS during the 1980s can be traced to the coincidence of new clinical and research observations, largely concerning possible links with infective agents and immune dysfunction, the changing nature of the relationship between doctor and patient (4), and consumer pressure. The consequence was immediate confusion about its definition and nosologic status. Most observers, invariably working in specialist centers, noted certain characteristics of their clinical samples. These included an overrepresentation of females and of persons from higher socioeconomic groups. Strong physical attribution and intense disease conviction were the norm (14, 20, 21), and certain professionals, such as doctors and teachers, seemed to be particularly at risk. In contrast, ethnic minorities were rarely encountered.

In 1988, David et al. (13) argued that the lack of information on the prevalence, nature, and etiology of CFS could be traced to the lack of epidemiologic data and neglect of epidemiologic principles in many of the published studies. Annual prevalence estimates then varied from 3 to 2,800 per 100,000 population. Since then, progress has been made in some areas, particularly in the realization of the need for uniform case definitions, but the neglect of epidemiologic principles such as selection bias and confounding continues to cause difficulties (22). Extraordinary variation in diagnostic practices remains. The diagnosis is made in anything between 1 in 60 to 1 in 10,000 Scottish general practice patients (23), while only one third of primary care physicians in St. Louis, Missouri, report seeing any cases at all (24).

At present, three operational case definitions have been presented. One started with the efforts of American infectious disease and immunology specialists (25) and has been revised on two occasions (26, 27). A second comes from an Australian group (28), and a third from a British consensus conference (29). These definitions are listed in table 1. There are a number of similarities, such as the requirement of substantial functional impairment in addition to the complaint of fatigue (although all definitions 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 a sore throat and painful muscles and lymph nodes; although the requirement for multiple symptoms has been modified in the latest definition (27), four somatic symptoms chosen from a list of eight are still required. The choice of symptoms reflects one school of thought which 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 the implications of these differences are, but all are purely operational criteria for clinical research, and none have any particular validity.

TABLE 1. Case definitions for chronic fatigue syndrome

	Minimum duration (months)	Functional impairment	Cognitive or neuropsychiatric symptoms	Other symptoms	New onset	Medical exclusions	Psychiatric exclusions
CDC*–1988	6	50% decrease in activity	May be present	Six or eight required	Required	Extensive list of known physical causes	Psychosis, bipolar disorder, substance abuse
CDC–1994	6	Substantial	May be present	Four required	Required	Clinically important	Melancholic depression, substance abuse, bipolar disorder, psychosis, eating disorders
Australian	6	Substantial	Required	Not specified	Not required	Known physical causes	Psychosis, bipolar disorder, substance abuse, eating disorders
United Kingdom	6	Disabling	Mental fatigue required	Not specified	Required	Known physical causes	Psychosis, bipolar disorder, eating disorders, organic brain disease

* CDC, Centers for Disease Control and Prevention.

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. Lewis and Wessely (17) reviewed 15 community studies and 10 primary care studies. They concluded that fatigue is one of the most common symptoms encountered in the community—it is, as another reviewer noted, "the normal chaff of living" (30, p. 486). In a subsequent British community survey, 38 percent of the sample reported substantial fatigue; fatigue had been present for over 6 months in 18 percent (31). In Germany, 26.2 percent of a population surveyed in Mannheim, Germany, complained of "states of fatigue and exhaustion" over a 7-day period (32). Similar figures are encountered in other Western countries (17).

Most fatigued people neither consider themselves ill nor consult a doctor (33, 34). Despite that, fatigue is a common symptom encountered in both primary and secondary care. A point prevalence of 21 percent for fatigue of 6 months' duration, associated with other somatic symptoms such as a sore throat, myalgia, and headache, was recorded in an American primary care survey (35). Thirty-two percent of those seen at an Israeli general medical practice reported at least one asthenic symptom (36). Slightly lower prevalence is reported in British primary care patients, where 10 percent will admit to chronic fatigue (37), and in Canada, where 14 percent of new patients complained of fatigue (38). It was the principal reason for consultation for 7 percent of new patients in primary care in both France and Canada (38, 39).

Relevant prevalence data can also be obtained from studies using the *International Classification of Diseases,* Tenth Revision (ICD-10) (40), criteria for neurasthenia, which overlap those for CFS considerably: 97 percent of persons visiting a multidisciplinary CFS clinic in Wales also fulfilled the criteria for neurasthenia (41)! In a Zurich, Switzerland, longitudinal survey, Merikangas and Angst (42) reported a prevalence of 6 percent for men and 10 percent for women. The recent multinational World Health Organization study of mental disorders in primary care reported a 5.5 percent prevalence of ICD-10 neurasthenia (43). In a longitudinal study carried out on the Swedish island of Lundby, the lifetime prevalence of fatigue syndrome (defined similarly to neurasthenia as excessive fatigue in the absence of clear-cut features of anxiety or depression) was 33 percent for women and 21 percent for men (44).

Whatever the label, all agree that physical investigations are rarely helpful, except in certain groups such as the elderly (45–47).

In an early study, 9 percent of 1,170 medical outpatients reported "tiredness, lassitude, or exhaustion" as principal complaints (48). Nearly 30 years passed before another systematic inquiry. In an examination of all symptoms experienced by hospital outpatients, one third of the people who visited one of two American ambulatory medical clinics reported fatigue (49, 50), making it the most common overall symptom, and it was the main reason for presentation in 8 percent (49). Routine investigations failed to identify a cause for nearly all of these subjects (49, 51), prompting the

publication of an editorial aptly titled "'Minor' Illness Symptoms: The Magnitude of Their Burden and of Our Ignorance" (52).

EPIDEMIOLOGIC DATA ON THE PREVALENCE OF CFS

Chronic fatigue is thus common, but what about CFS? On the basis of laboratory request forms, Ho-Yen (53) estimated the prevalence in the west of Scotland as 51 per 100,000 population. The first attempt at a population-based study using an operational case definition came from Lloyd et al. in Australia (28). Cases were identified using general practitioners as key informants. A point prevalence of 37 per 100,000 population was recorded. However, only 25 percent of the physicians approached agreed to participate. Ho-Yen and McNamara (54) achieved a better response rate in their survey of Scottish general practitioners. They estimated a prevalence of 130 per 100,000 population, but recognition of CFS varied. Professional workers remained overrepresented, although this could still reflect differences in labeling. CFS consumed considerable amounts of medical time. The Centers for Disease Control and Prevention (CDC) attempted to estimate the prevalence of CFS on the basis of surveillance of selected physicians in four US cities (55). The observed prevalence of CFS was lower than the Australian figures—2–7 per 100,000 population. 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.

Price et al. (56) used the Epidemiologic Catchment Area data (collected before the upsurge of interest in CFS) to develop approximations of the original CDC criteria. Only 1 of 13,538 people (7 per 100,000 population) fulfilled the approximate criteria, which were looser than the full CDC criteria. Most of the possible cases were excluded because of the overzealous physical and psychological exclusions mandated by the 1988 CDC definition.

Recent studies with systematic case ascertainment reported a different picture. Bates et al. (50) surveyed an American ambulatory care clinic at an academic teaching hospital. In keeping with the literature, 27 percent of those visiting the clinic had had substantial fatigue lasting for more than 6 months and interfering with daily life. The point prevalence of CFS according to the various definitions was 0.3 percent (1988 CDC criteria), 0.4 percent (United Kingdom), and 1.0 percent (Australia), respectively. Of an occupational sample, 0.9 percent met the criteria for CFS (57). A questionnaire-based study of subjects registered with a single Scottish general practice (58) reported a point prevalence of 0.6 percent (95 percent confidence interval 0.2–1.5) according to the UK criteria, but this was based on only four cases. This author and his colleagues found even higher prevalences in a follow-up study of 2,376 subjects aged 18–45 years who had been seen in one of five general practices across the south of England (59). The prevalence of CFS ranged from 0.8 percent (1988 CDC criteria) to 1.8 percent (1994 CDC criteria). The permeable nature of UK primary care implies that these figures can be used to approximate community point prevalence.

These primary care figures are an order of magnitude greater than those obtained during the first wave of primary care and community surveys. Why? The answer is that nearly all of those who fulfilled operational criteria for CFS were not labeled as having such by either themselves or their general practitioners, and thus would not have been identified in a key informant survey or a tertiary care setting (59). Among the vast numbers of subjects with excessive fatigue, only 1 percent believed themselves to be suffering from CFS (60). Among the smaller numbers who fulfilled the criteria for CFS, only 12 percent used this term or a related term to describe their illness (59). A preliminary communication by Jason et al. (61) from Chicago, Illinois, reports that only 25 percent of persons identified as possible CFS sufferers in a random telephone sample thought they had CFS. This emphasizes that, even in the United States, few of those who could be classified as having CFS are actually labeled as having it. This also highlights the powerful role of selection bias in previous studies, which were almost all based on tertiary care samples of patients who had frequently made their own diagnosis before seeking specialist help, and were almost certainly an atypical and unrepresentative sample of CFS cases (22). Quasi-epidemiologic data obtained using general practitioners or hospital physicians as "key informants" clearly have limitations. Systematic surveys are beginning to suggest that CFS and/or neurasthenia represents a substantial but neglected public health problem.

THE ROLE OF PSYCHOLOGICAL DISORDERS

As an isolated symptom, fatigue is strongly associated with psychological distress, frequently preceding the development of major depressive disorder in primary care (62). Fatigue alone was associated with adjusted odds ratios of 2.6 (women) and 6.8 (men) for subsequent major depressive disorder 1 year later (63).

Depression and anxiety are the most robust associations of chronic fatigue in primary care (64, 65). The presenting symptoms of sleep disturbance, fatigue, multiple complaints, and musculoskeletal symptoms,

all of which are common in CFS, were the best discriminators between depressed and nondepressed primary care subjects (66). Seventy-two percent of those with excessive chronic fatigue seen in primary care were assigned a psychiatric diagnosis according to the ICD-9 (67, 68); the relative risk for psychological disorder and chronic fatigue in another community survey was 6.0 (58).

Turning to CFS, numerous studies have been published concerning the role of psychiatric disorders in CFS, 11 of which used direct interviews (see David (69) and Clark and Katon (70)). 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 form of CFS or another fulfill criteria for an affective disorder, even with fatigue removed from the criteria for mood disorder. The majority of studies find that a further quarter fulfill criteria for other psychiatric disorders, chief among which are anxiety and somatization disorders. Nearly all also agree that between one fourth and one third do not fulfill any criteria. Conversion disorder, a preoccupation of the media, is rare. Figures for comorbidity between neurasthenia and psychiatric disorders are also congruent with these findings: In the multinational World Health Organization study of mental disorders in primary care (43), ICD-10 neurasthenia showed 71 percent psychiatric comorbidity.

These studies have been discussed at length elsewhere (69, 70). Four explanations for the findings have been suggested. The first is that the observed psychological distress is solely a reaction to physical illness. However, studies that compared rates of psychiatric disorders in CFS patients with those in medical controls found that the risk of psychiatric disorder was elevated in the CFS cases (14, 71–73). This argument also assumes that discrete physical pathology and symptoms have already been identified, a premature claim. The second explanation is misdiagnosis of psychiatric illness. The third explanation suggests a common origin for both CFS and psychiatric disorder, the result of overlapping neurobiologic processes (see Demitrack and Greden (74)). There is a rapidly expanding body of literature on the results of neuropsychological and neuroimaging investigations of CFS which lies beyond the scope of this review but lends support to this position. In particular, a pattern can be discerned in which CFS is associated with a disorder involving effortful cognition, just as it is associated with an increased sense of motor effort. The fourth explanation for the association between CFS and psychological morbidity is that it is an inevitable artifact 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 raises the question of whether or not psychological disorders, past or present, should be excluded from the diagnosis of CFS as they are from the current concept of neurasthenia. Excluding CFS on the basis of past psychiatric illness has considerable drawbacks. In the CDC study (55), 45 percent of those who would otherwise have fulfilled the CFS criteria were excluded because of prior psychiatric disorders, yet in other respects they resembled the full CFS cases (and no doubt believed that they too had CFS). It assumes that previous psychiatric illness excludes a diagnosis of CFS, although some (but not all) tertiary care studies suggest that it may be a risk factor. Neither 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. At present, it seems safest to exclude only those patients with clear evidence of a current or recent psychiatric disorder that seems to have little relevance to the spectrum of CFS (eating disorders, substance abuse, psychosis). A good case can also be made for excluding subjects who fulfill the criteria for somatization disorder (75).

SEX

Nearly all published studies report that women are overrepresented in specialist samples of CFS. There are few clinical differences between CFS as it is found in men and CFS in women (76). Many authors suggest that sex differences observed in clinical samples could be an artifact of illness behavior and referral. Although few community-based studies report an equal sex distribution for chronic fatigue or CFS (an exception being a recent study of 4,000 members of a health maintenance organization (77)), the sex differences observed in population-based studies are considerably more modest than those found in specialist samples. In one community study, the relative risk of fatigue in women as compared with men was 1.3 (60). In primary care settings, the relative risk for women varies between 1.3 and 1.7 (37–39).

There is an obvious similarity between these findings and those reported for sex 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 (78). Affective disorder is well known as having one of the strongest associations with fatigue. However, although controlling for depression removed the sex difference

in fatigue in one community study (79), this was not found in two other studies (31, 60). Pawlikowska et al. (60) noted that as various restriction criteria of increasing stringency were applied (such as duration, percentage of time the patient was tired, presence of myalgia), the female : male ratio of cases increased.

INFECTION

Many patients encountered in specialist care settings, including infectious disease clinics (80), immunology clinics (81), neurology centers (14, 82), and fibromyalgia clinics (83), report that their illness followed an apparent episode of infection, which is reflected in one of the current synonyms for CFS, "postviral fatigue syndrome." However, there are a number of methodological reasons why such associations should not be accepted uncritically (84, 85). Viral infection is extremely common in the community: Up to one third of the population will reply positively to a question asking whether they experienced a viral infection during the last month (31). One cannot exclude the possibility of chance associations between viral infection and the onset of fatigue. The techniques used to detect previous exposure to viral infection in patients with illness of long duration are very prone to error. Search-after-meaning and recall bias are also relevant, since there are psychological and social reasons why people may prefer to attribute their fatigue syndrome to a virus as opposed to 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 (see Straus (86)). Claims have also been made for another herpes virus, human herpes virus 6. Human herpes virus 6 infection is ubiquitous, rendering interpretation of serologic studies difficult, but a recent review concluded that while it was an unlikely etiologic candidate, secondary reactivation by some other mechanism or by stress might contribute to symptoms (87). Claims of a retroviral etiology for CFS were made in a blaze of publicity, but appear to have been premature.

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 have been faulty. However, the interest generated by these findings was sustained with the introduction of newer tests, both serologic and molecular. Better-designed studies again showed equal levels of exposure in cases and controls for these probes as well (88–90). At present, there is no compelling evidence for enteroviral involvement in CFS. Finally, in a controlled prospective study of the outcome of over 1,000 symptomatic infective episodes seen in British primary care patients, we have been unable to demonstrate any link between clinical viral infection and subsequent chronic fatigue or CFS (91).

Researchers have thus learned to be more cautious about overenthusiastic espousal of links between specific infections and CFS. The possibility of infective triggers for CFS does remain on the agenda. Clinical evidence of CFS arising after infection with a number of different agents—viral, bacterial, and even protozoal—suggests that the condition is more likely to represent a nonspecific response to a number of infective (and noninfective) agents than to be solely attributable to any single agent (92–94), although prospective longitudinal studies with adequate controls are few and far between.

At present, epidemiologic data do not confirm a link between CFS and the common infective agents encountered in everyday life. However, a population perspective cannot exclude the possibility of a rare reaction to a common infection or, alternatively, a common reaction to an unusual agent. At the time of this writing, sound epidemiologic data had been presented for only one single agent, which, ironically given some researchers' discounting of the possibility, is the Epstein-Barr virus. A recent prospective longitudinal primary care study of the outcome of Epstein-Barr infection demonstrated that Epstein-Barr and non-Epstein-Barr glandular fever are associated with a postinfectious fatigue syndrome that can be distinguished from depression, and that does not arise after simple respiratory tract infection (94). Six months after onset, the relative risk of fatigue syndrome after Epstein-Barr- and glandular fever-like infections, as compared with ordinary respiratory tract infections, is 5 (94).

IMMUNE DYSFUNCTION

Great attention has been paid to the role of possible immune dysfunction in CFS, either as the primary cause of the syndrome or as a consequence of some other process such as chronic infection (95). There is evidence of laboratory abnormalities, with the most consistent findings emerging from studies of T-cell subsets (96). Problems in interpretation remain, including nonspecificity and lack of a relation to clinical findings (97). The role of potential confounders, such as inactivity and psychiatric morbidity, also remains unclear (95). A case-control study conducted in a specialist care setting reported higher rates of atopic disorder (98). No reported allergic or immunologic abnormalities can, as yet, be placed in an epidemiologic context.

SOCIAL CLASS

It would be tedious to list all of the studies which have found that CFS patients visiting specialist care centers or self-help groups are more likely to come from upper socioeconomic strata. The self-diagnosis of CFS is associated with social class and with certain professions, particularly health care and teaching, while ethnic minorities seem to be underrepresented. Of the 3,000 individuals who telephone the CDC's CFS information line every month, one fourth are medical or paramedical professionals (99). Occasionally, an 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 among the ranks of neurasthenia sufferers (3, 100)) are unconvincing, with the possible exception of Epstein-Barr virus infection, since lower socioeconomic status is associated with an increased risk of primary Epstein-Barr infection in childhood (101). Other explanations include differential access to health care and differential labeling by both sufferers and doctors.

In contrast to the pattern observed in specialist samples of CFS patients, there is no evidence of any excess of higher socioeconomic status persons with fatigue, chronic fatigue, or CFS observed in the community or in primary care settings, nor is there evidence that ethnic minorities are less at risk (28, 31, 38, 57, 59). Systematic surveys also provide no support for the idea that health care workers are more vulnerable to chronic fatigue or CFS (37, 58).

SELECTION BIAS AND ILLNESS BEHAVIOR

The majority of cases of CFS seen in specialist practices also fulfill criteria for psychological disorders. How much is this a real association, and how much does it represent referral bias and the influence of psychological morbidity on illness behavior? An analogous situation is that of irritable bowel syndrome. In cases of irritable bowel syndrome seen in gastroenterologic practice, there is a consistent relation with psychological disorders such as depression and anxiety. This relation is far weaker in community cases of irritable bowel syndrome, suggesting that the links between irritable bowel syndrome and psychological morbidity observed in clinical practice are a product of illness behavior and referral patterns (102, 103).

The pattern is more complex in CFS. Subjects fulfilling criteria for CFS seen in primary, secondary, and tertiary care settings differ in many ways, but the prevalence of psychological disorders is high in all settings, with only some suggestions of slightly decreased rates in the community or in primary care (39) (although the pattern and severity of psychological morbidity almost certainly differ by sample (14, 67)). This author and colleagues have found that, even in primary care, introducing the more restrictive criteria for CFS strengthens, not weakens, this association (104), as has already been described in tertiary care (105). Thus, the links between CFS and psychological disorders are inherent in the choice of diagnostic criteria, but they may be further strengthened by selection bias and illness behavior.

The overlap between psychological disorders and CFS is not 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 (106, 107). Similarly, the greater the number of pain symptoms, the greater the risk of depression (108). One of the salient features of CFS patients is that they experience not only fatigue but a variety of other somatic symptoms as well (109). 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 (14, 71, 109, 110). Current concepts of CFS emphasize its polysymptomatic nature (25, 27): Persons fulfilling its criteria have more functional somatic symptoms than fatigued patients who do not meet the criteria.

Katon and Russo concluded that "the patients with the highest numbers of medically unexplained physical symptoms had extraordinarily high rates of current and lifetime psychiatric disorders" (105, p. 1604). In a community study of 15,283 subjects (60), we noted a close and linear relation between fatigue and psychological disorders as measured by questionnaire. In a subsequent primary-care study, we found a similar close relation between the risk of a psychiatric disorder, measured by questionnaire or interview, and the number of somatic symptoms (either all symptoms or just those endorsed by the CDC) (104). The latest definition from the CDC (27), which continues to emphasize 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 be just as logical to have a *maximum* (rather than a minimum) number of nonfatigue symptoms and, on the other, concepts of CFS as a specific disease entity resulting from an as-yet-undiscovered pathologic process.

Studies showing that fatigue and exhaustion are among the cardinal features of affective, anxiety, and somatization disorders are too numerous to mention. Nevertheless, the links between CFS and these disorders should not 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 . . ." (111, p. 161). The same criticisms and limitations identified for CFS apply in equal measure to the operational definitions currently being used for common psychological disorders. Links with operationally defined psychiatric disorders should also not obscure the considerable variation and heterogeneity within psychiatric diagnostic categories themselves. In particular, there is neuroendocrine evidence from specialist centers which suggests that one subgroup of CFS patients can be distinguished from persons with major or melancholic depression (74, 112).

CFS AND THE SPECTRUM OF FATIGUE

So far, it has been assumed that fatigue is something which one either has or doesn't have. This dichotomous approach is an essential prerequisite for determining conventional epidemiologic 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, or between chronic fatigue and CFS?

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?' " (113, p. 873). With regard to mental disorders, Goldberg and Huxley 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" (107, p. 58). The same could be argued for fatigue. Several studies from primary care settings or the community now suggest that fatigue and related asthenic symptoms are indeed continuously distributed (17, 37, 60).

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 of the viewpoint from the measurement of discrete states of fatigue to continuous determinations of susceptibility" (114, p. 354). However, in the current political climate surrounding CFS, it is important to note that this dimensional view of fatigue no more invalidates the illness status of CFS 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 to view himself 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. At the extreme end of this spectrum are small numbers of patients with the most extreme disability, the worst prognosis, and the greatest chance of fulfilling the criteria for somatization disorder (75).

Only a minority of persons with chronic fatigue fulfill the criteria for CFS (50, 67, 71, 115)—but these people 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 (116, 117). 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 pheochromocytoma, but it is the role of population-based studies to place these cases in their epidemiologic context.

CONFOUNDING

It has already been noted that patients seen in specialist settings or recruited from self-help groups may be atypical in terms of social class. They have generally also been ill for a long time. The mean duration of illness was 5 years among patients referred to a neurologic hospital (14) or an immunology clinic (81), 7 years in the CDC study (55), and 13 years among persons visiting a special fatigue clinic (118). CFS cases recruited from these settings (where nearly all etiologic studies have originated) have considerable morbidity enshrined in the current definitions of CFS, all of which insist on functional impairment. Being completely confined to bed is not unusual. This is relevant, because lack of physical activity has profound effects on muscle function and chemistry as well as on cardiac function, but it may also affect both immune and psychological status. Particularly relevant is the fact that lack of activity is itself a risk factor for fatigue (79, 119, 120), which may set up a vicious circle of inactivity and impairment (see Klug et al. (121) and Wessely and Sharpe (122)). Studies of CFS have reported abnormalities in many aspects of neuromuscular, cardiac, immunologic, and psychological functioning, yet the possible confounding role of inactivity is not always addressed.

PUBLIC HEALTH IMPLICATIONS

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 the patients who admitted tiredness, 26 percent said it had forced them to restrict their normal activities, and 28 percent reported needing to lie down in response to the symptom (34). In another study of primary care patients, Nelson et al. 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" (123, p. 184). Twenty-eight percent of patients with chronic fatigue have been completely bedridden at some stage (35). In our primary care study, chronic fatigue subjects had worse mental health, more physical pain, a worse perception of their health, and greater physical impairment than nonfatigued controls. For comparison, data from the Medical Outcomes Study (124) showed higher scores (indicating better functioning) for subjects with diabetes, hypertension, and arthritis. Only patients with angina and advanced coronary artery disease scored lower. The mean level of role functioning for chronic fatigue patients was substantially lower than that for persons with hypertension or diabetes, and again only advanced coronary artery disease patients scored lower.

Functional impairment in full-blown CFS is even more profound (59, 125). This is partly artifactual, because functional impairment is a requirement of all of the current definitions, but in one study impairment remained profound even when this requirement was removed from the operational criteria employed (59). Functional impairment was also closely linked to psychological morbidity. The World Health Organization study found an association between psychiatric comorbidity and functional disability in neurasthenia patients (43).

PROGNOSIS

The prognosis of chronic fatigue in tertiary care is gloomy. At the Mayo Clinic (Rochester, Minnesota), 235 patients with a diagnosis of chronic nervous exhaustion were followed up approximately 6 years later (126). Most remained symptomatic, although precise figures were not given. One hundred and seventy-three cases of neurocirculatory asthenia seen by a single cardiologist were followed up for an average of 20 years (127). Only 11 percent of the patients were asymptomatic at follow-up, while 38 percent were mildly disabled and 15 percent were severely disabled.

Little has changed with the arrival of CFS. Behan and Behan write that "most of the cases seen do not improve, give up their work, and become permanent invalids" (82, p. 164). Only 18 percent of those referred to a Belfast, Northern Ireland, clinic improved (81), and only 13 percent of those seen at an infectious disease clinic in Oxford, England, considered themselves fully recovered 2 years later, although more of them had improved (128). Only 6 percent of subjects who took part in treatment studies in Australia had fully recovered after 3 years (129). The Oxford and Sydney, Australia, groups both reported that the strongest association with failure to recover was the strength of the patient's belief in a solely physical cause of symptoms, as well as the presence of a psychiatric disorder (128, 129). 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 and Sharpe (122) and Abbey (130) for reviews).

OTHER FATIGUE SYNDROMES

No mention has yet been made here of a variety of other syndromes commonly seen in medical practice in which fatigue is a prominent symptom. These include fibromyalgia, irritable bowel syndrome, effort syndrome, hyperventilation syndrome, and the various so-called allergy or chemical sensitivity syndromes. In all of these illnesses, not only is fatigue prominent but so also are many of the other somatic symptoms found in CFS. Few systematic studies have addressed these issues, but it is probable that there is substantial overlap between these various syndromes (131). Choosing the diagnosis for such patients may be an arbitrary process, influenced by such factors as the patient's presenting complaint and local referral practices.

THE SOCIAL PURPOSE OF CFS

Dohrenwend and Crandell (132) used instruments derived from the Midtown Manhattan Study, a classic piece of psychiatric epidemiology, to study professional and nonprofessional attitudes toward common symptoms. Doctors and patients were found to regard different symptoms with differing degrees of concern. "Feeling weak all over much of the time" was regarded as "very serious" by only 6 percent of psychiatrists and 9 percent of physicians, making it one of the least important of 43 listed symptoms (132). In contrast, the same symptom was listed as one of the most important by nonprofessional samples. These differences are understandable: Doctors, aware of the nonspecificity of fatigue, focus more on specific complaints such as hemoptysis or self-harm. On the other hand, patients experience it as disabling, distressing,

and perhaps of sinister significance. This difference in importance given to fatigue by patients and professionals is mirrored by a second division. Whereas doctors working in primary care are most likely to record psychological diagnoses in patients presenting with new episodes of fatigue, patients are more likely to view the same episodes as being of physical origin (133). These possible sources of misunderstanding arising between doctor and patient are magnified by the social stigma associated with having a psychiatric disorder. These and other cultural factors, such as popular beliefs about the role of viruses, immunity, and the environment in health and disease, have contributed to the current prominence of CFS (5, 134). In consequence, CFS has now become an illness "that cannot be debated dispassionately" (135, p. 383), surrounded by a "highly charged medical, social, and political atmosphere" (136, p. 343).

CONCLUSIONS

In this review, the author has attempted to outline what we do and do not know about the epidemiology of CFS. There are several questions facing researchers interested in this condition. First, can the many reports of abnormalities of immunologic, infective, and neurobiologic functioning be placed in an epidemiologic context? Second, what are the similarities, and differences, between patients with CFS seen in specialist care settings (the bulk of studies to date) and those fulfilling the same criteria in the community or in primary care? Knowing this would assist us in determining which of the many features of CFS are intrinsic to the condition and which result from social and cultural pressures that accompany the diagnosis. A related topic is the need to distinguish between the epidemiology of an operationally defined condition and that of an illness belief (57, 134). Third, what is the relation between subjects who fulfill the consensus criteria and those who do not? There is already a suggestion that nonsyndromal cases resemble full-blown cases. If this is so, this continues to cast doubt on the external validity of current categorical case definitions of CFS. Fourth, what are the possibilities of genetic epidemiology in establishing associations between CFS and other related conditions?

Finally, a remaining question is that of the relation between CFS and comorbid CFS. It has already been suggested that CFS is accompanied by high rates of comorbid psychiatric disorders, and that psychiatric illness is associated with functional impairment. However, no study has ever reported complete congruence between CFS and psychiatric disorders. Do the associations with CFS differ according to the presence or absence of comorbidity? There are two lines of evidence suggesting that this might be so. The first is the data from studies of neuroendocrine function, mentioned above (74, 112, 137). The second comes from the important cohort study carried out by White et al. (94) on the outcome of Epstein-Barr and Epstein-Barr-like infections. Acute social adversity was strongly associated with the development of depression after glandular fever. However, "pure" postinfectious fatigue syndrome (i.e., without comorbid depression) was not associated with life events (138). The implication is that acute social adversity predicts psychological comorbidity rather than fatigue syndrome per se. It will be interesting to see whether this finding can be replicated for fatigue syndromes that arise in situations other than after glandular fever.

CFS represents a considerable challenge to epidemiology. Although it is a difficult area for study, it is nevertheless of great public health importance. There is also the tantalizing possibility that well-conducted studies will shed light not just on the subject of CFS but also on other disorders that lie in the gray area between medicine and psychiatry.

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