Chapter 21

Viruses and Fatigue

The Current Status of the Chronic Fatigue Syndrome

Simon Wessely

INTRODUCTION

Perhaps none of the subjects covered in the last edition of this book have changed so quickly as the vexed topic of "postviral" fatigue. When James Jones and Bruce Miller (Jones and Miller, 1987) reviewed the situation, the general theme was one of optimism, and despite an awareness of remaining uncertainties and difficulties, progress in understanding the relationship between viruses and chronic fatigue states was anticipated. Sadly, in the subsequent 3 years little of this optimism has been realized. Even the title of the current contribution is different, reflecting increasing international skepticism concerning the exclusive role of viruses. The new term favored for the condition is "chronic fatigue syndrome" (CFS) (Holmes *et al.*, 1988; Lloyd *et al.*, 1988a), as it is accurate, short, and carries no unproven etiological implications. It will be used in the rest of this chapter to refer to the various illnesses described as "myalgic encephalomyelitis" or "Royal Free Disease" in Britain and Australia, and "chronic Epstein–Barr virus infection" or "chronic mononucleosis" in the United States.

The current hypothesis underlying CFS is simple: that a viral illness is a cause

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chronic active EBV infection, or viral cardiomyopathy will not be discussed further. Finally, there is now a rapidly growing literature on fibromyalgia, a condition with considerable relevance to CFS, but in Britain at least, largely ignored. This serves further to emphasize the unsatisfactory nature of current case definitions.

Selection Bias

Nearly all published studies suffer from several selection biases, of which the most serious is selection by exposure under investigation. In all case–control studies it is fundamental that the ascertainment of cases of disease is independent of exposure status (Rothman, 1986). In the studies of postviral fatigue, the diagnosis of disease ("postviral fatigue") is frequently influenced by a knowledge of exposure (history of viral infection). In two studies (Yousef *et al.*, 1988; Hotchin *et al.*, 1989) that show an association between serological markers of infection (enterovirus and EBV, respectively) and postviral fatigue, people became cases because of their exposure status. Patients were recruited by the medical adviser to a self-help organization for people with "postviral fatigue." Many of these patients felt they had been exposed to a virus, otherwise they would not have joined that particular organization. The medical adviser recruiting patients (and controls) was also aware of exposure status, so it is possible that further selection took place at this stage, such as the exclusion of those lacking a history suggestive of a viral illness (the opposite occurring for neighborhood controls). Cases are in effect being selected by a risk factor which is then being measured. In view of the overlap between exposure status and ascertainment of cases and controls, the finding of differences between "cases" and "controls" is difficult to interpret.

Selection bias also operates long before the patient reaches the research team. The symptoms of fatigue are common, so general practitioners may be more likely to refer to centers with an interest in postviral fatigue patients with a history of infection, which may or may not be relevant. For example, studies of chronic EBV infection have used "highly selected patients referred to investigators known to have an interest in chronic EBV infection" (Buchwald *et al.*, 1987). Depressed patients with prominent fatigue and sleep difficulties are more likely to be referred to physicians than those presenting with more obvious cognitive features such as guilt and suicidal ideation (Dew *et al.*, 1988).

Bias is also introduced by social class. The symptom of chronic fatigue shows a negative socioeconomic gradient in community studies (Cox *et al.*, 1987). However, nearly all current work on CFS acknowledges a positive socioeconomic gradient, with an overrepresentation of upper social classes, in particular health service professions. Indeed, this has led to the unpleasant term "yuppie flu" (Seligmann *et al.*, 1986). Such a label, even if perjorative, implies that this is a new finding. However, this is not so (Wessely, 1990b). Savage (1875) reported that

fatigue was commonest in professions requiring an unflagging devotion to work, or a high degree of emotional stress. Since then, the overrepresentation of higher social classes has been a constant finding (Taylor, 1907; Dowden and Johnson, 1929; Macy and Allen, 1933–1934). Kraepelin (1902) described neurasthenia, the forerunner of CFS, as "one of the products of civilisation, confined largely to the professional and clerical callings, and to women of the middle classes." Such historical evidence disproves the occasional attempt to link this syndrome with various "toxic" agents encountered in modern life (Hall and MacPhee, 1985). It also indicates further bias in published studies based on such samples, which is almost certainly the result of social class differences in health care utilization.

Information Bias

The commonest information bias is the absence of data concerning psychological symptoms. In studies that have looked for them, emotional symptoms, however defined, are intimately associated with fatigue states, for example occurring in 80% of a series of 500 patients (Behan and Behan, 1988). However, many studies make no mention of any psychological variables. Others acknowledge that emotional symptoms are almost invariably present (Fegan *et al.*, 1983; Bell *et al.*, 1988b), but do not collect this information systematically, or use it in a meaningful way. A recent editorial on lassitude (Havard, 1985) stated that "failure to diagnose depression is usually due to failure to seek it rather than to any confusion in diagnostic symptoms."

Further difficulties are the overlap between the symptoms of depression and those of viral infection. If the two occur in sequence (either in consequence or by chance), it is difficult for the doctor, let alone patient, to distinguish between them. In these circumstances it is easy to conclude, often erroneously, that an infective episode is still continuing (Imboden, 1972).

Recall Bias

Recall bias adds further inaccuracy. Patients who believe they have the disease are highly motivated to remember their viral illness, as they attribute this as the cause of their troubles. An inadvertent example of this is provided by Meijer *et al.* (1988). In a study of the relationship between influenza and psychiatric disorder in adolescents, those with greater psychopathology were more likely to report a previous episode of influenza. The authors conclude this is evidence for "post-influenzal psychiatric disorder." However, there were no differences in the levels of influenza antibody between cases and controls. Instead, psychiatric disorder may have caused those affected to be more likely to recall clinical influenza, although this was not confirmed in a new population study (Wessely, unpublished data).

Measurement Bias (Difficulties in Ascertaining Exposure)

If it is difficult to define the disease state, it is almost as difficult to define the presumed exposure, a viral infection. Both within subject variability and observer variability have been noted.

The levels of detectable antibody to many viruses, including EBV, are altered by many confounding factors. Of particular relevance is that stress alone can alter EBV titers (Kiecolt-Glaser *et al.*, 1984). Virtually any chronic stress or intercurrent illness has the capacity to reactivate latent infection or cause an amnestic antibody response, as will any cause of lymphocyte activation (Johnson, 1982). The use of normal controls may be inappropriate in case–control studies of CFS (Straus, 1988; Wessely and Powell, 1989).

Turning to observer variation, many laboratories use different standardizations, and there is evidence of poor reliability within and among laboratories (Holmes *et al.*, 1987). Determination of immunofluoresence depends upon "subjective interpretation of visualised fluorescence" (DeLisi *et al.*, 1986), and is subject to the difficulties in reliability inherent in all bioassays (Merlin, 1986). Finally, it is well known that many clinically apparent viral infections cannot be detected by the available laboratory tests; false-negatives are a problem in addition to false-positives.

Case–Control Studies: Conclusion

Case–control studies are a valid method of estimating the relative risk of an exposure such as a viral illness, provided that both cases and controls are representative of a defined population, and that case selection is independent of exposure. It is clear that neither of these rules has been adhered to in some of the studies reviewed. Most of these biases are not random, and result in overestimation of the relationship between exposure to viruses and fatigue.

Case–control studies, even if correctly executed, may not be the most appropriate for this problem. They are restricted to one particular clinical problem, the disease nominated by the investigator. As it is empirically unlikely that a single infectious agent will be associated with only one outcome, a more powerful design is to define exposure, and then look at a number of possible disease outcomes over time, as in a cohort study. The few studies that conform to this design will be reviewed later.

David *et al.* (1988) have pointed out the problems in case definition, and advocated the use of operational criteria. Since then, although not as a result, at least three case definitions have been published. Unfortunately, problems still remain.

The current operational criteria propose a mixture of clinical and laboratory data, using major and minor criteria analogous to the Duckett–Jones criteria for

rheumatic fever (Holmes *et al.*, 1988; Lloyd *et al.*, 1988a). These are useful, as at least they will permit comparisons to be made, but are only as good as the component parts. Already problems have arisen as the rules may be too restrictive: in one study of those who clinically appeared to have chronic fatigue, only 5% of patients fulfilled the criteria (Manu *et al.*, 1988b), the majority being excluded as cases of psychiatric disorder. Recognition that criteria excluding psychiatric disorder may be throwing out the baby with the bath water led to recent alterations in the operational criteria (Komaroff *et al.*, 1989). Operational criteria are an improvement, but to state that the disease is a "common, discrete and easily diagnosable clinical illness" (Bell and Bell, 1988) is both optimistic and inaccurate.

WHAT IS THE RELEVANCE OF EXPOSURE TO DISEASE?

Epidemiology of Viruses and Fatigue

First, the association between viruses and fatigue may be a chance one. Considering just enteroviruses alone, the average individual has between one and four infections per year. Subclinical infections are commoner, and the majority of Coxsackie virus and echovirus infections are not associated with significant clinical problems (Johnson, 1982); indeed, the ratio of infected individuals to known serious clinical cases is 1000:1 (Pallansch, 1988). Commonest of all are self-reported viral infections. Between 25 and 40% of adults felt they had suffered a "cold or 'flu' " in the previous month (Cox *et al.*, 1987), compared with a previous finding of 32% for "cold" and 18% for "influenza" (Dunnell and Cartwright, 1972). The United States National Health Survey listed annual rates of various viral infections: for combined age group 18–44 the total was 90 viral infections per 100 people. In both studies there is a steady fall from peak values in late adolescence (which does not match the age distribution of fatigue).

Turning to fatigue, there is no doubt that the symptom is also widely distributed in the population. Henry Miller (1987) has aptly described "The vague sense of being under the weather is what most people, if asked, will admit to most of the time." Translated into epidemiological terms, this becomes "the fact that a large proportion of the population has the occasional symptom of dysphoria, fatigue or insomnia probably accounts for the high rates reported by earlier surveys" (Goldberg and Huxley, 1980). However, more modern studies have shown that chronic fatigue, arbitrarily defined as more than 1 month in duration, still occurs in between 20 and 30% of the population (Chen, 1986). For example, Kroenke *et al.* (1988) surveyed 1159 consecutive clinic attenders. Cases were those who felt that fatigue was a "major problem" for 1 month, although the mean duration was actually 3.3 years, and the overall prevalence was 24%. As in all other studies, chronic fatigue was commoner in women than men. Buchwald *et al.* (1987) were surprised to find

that 21% of all practice attenders satisfied their criteria for "chronic EBV" syndrome. In the first systematic study of psychiatric illness in general practice in the United Kingdom (Shepherd *et al.*, 1981), 16% of males and 24% of females admitted to rising in the morning feeling tired and exhausted, while similar percentages felt that working tired them completely. These figures rose when the sample was restricted to those with psychiatric diagnoses, and rose again in a sample of psychiatric outpatients. Better primary care studies are needed, and although we cannot conclude that all such patients have CFS, but it is already clear that patients with chronic fatigue in both primary care and general hospitals experience personal morbidity and functional impairment similar to that found in chronic medical patients (Kroenke *et al.*, 1988; Wessely and Powell, 1989).

Given the high prevalence of both chronic fatigue and self-reported viral infections, the association of any cause of fatigue and a viral infection will occur by chance in a large number of people. It has also been shown that this figure will be elevated by such factors as selection and recall bias. Samples selected from either self-help groups, or referred to centers with a known interest in CFS, will inevitably contain an overrepresentation of those in whom the association between viruses and fatigue has occurred by chance alone. Such sampling bias will not be corrected by comparison with normal controls.

EBV and CFS

In the United States, but not in the United Kingdom, there has been intense professional and media speculation concerning a possible link between CFS and EBV. However, after initial enthusiasm following the publication of several studies reviewed by Jones and Miller (1987), such optimism is now giving way to pessimism. The marker originally thought to indicate continuing chronic EBV infection was antibody to the early antigen (EBV-EA) (Tobi *et al.*, 1982; Straus *et al.*, 1985). One U.K. study has found antibody to EBV-EA elevation in 20% of selected cases of CFS (Hotchin *et al.*, 1989). However, it is known that many asymptomatic patients continue to show such antibody for 2 to 4 years after full recovery from EBV (Horwitz *et al.*, 1985). Hellinger *et al.* (1988) were unable to find clinical differences between patients with or without EBV-EA antibody, and also found EBV-EA antibody in 18% of asymptomatic blood donors at the Mayo Clinic, with extreme elevation (greater than 1 in 160) in 3%. Similarly, Buchwald *et al.* (1987) found EBV-EA elevation to levels they had previously regarded as abnormal in 43% of controls. The role of EBV nuclear antigen (EBV-NA) is still unclear: lack of antibody to the nuclear antigen remains a possible association of CFS.

Some (Holmes *et al.*, 1987), but not others (Hotchin *et al.*, 1989) report not only elevated titers to EBV, but also to cytomegalovirus, herpes simplex, and measles. There is also no evidence of increased viral burden based on direct assessment of viral load (Schooley, 1988). Finally, there is no evidence of any

relationship between clinical symptoms of fatigue and laboratory findings, nor between clinical recovery and the resolution of any serological or immunological abnormalities, even in patients specifically selected for serological abnormalities (Schooley, 1988; Straus *et al.*, 1988; Katon *et al.*, 1988). The current consensus is that EBV serology has no obvious place in the diagnosis of CFS (Straus, 1988; Borysiewicz, 1989).

Coxsackie Viruses and CFS

In the United Kingdom, attention has been focused on the role of the Coxsackie viruses in the etiology of CFS. These are promising candidates, in view of their known myo- and neurotropic actions. Furthermore, interpretation of serological findings is less complex as neither latency nor reactivation has yet been demonstrated. Although previous serological tests have been unsatisfactory, this too has recently changed. The development of an ELISA test for Coxsackie IgM (Bell *et al.*, 1988a) promised a better measure of current or recent infection. It was found in 5–9% of community controls (Bell *et al.*, 1988a). In a hospital series, enterovirus IgM was detected in 31% of cases of CFS, compared to 12% of controls (Banatavala and Muir, personal communication). However, a case–control study of CFS in primary care apparently failed to show any difference in Coxsackie antibody titers between cases and controls (Dawson, 1987).

So far the main evidence is provided by the study of Yousef *et al.* (1988). They reported that 17/76 (22%) of patients referred with postviral fatigue syndrome had enteroviral infection demonstrated by positive stool cultures, which persisted in 5 at 1 year (7%). This is conventional evidence of persistent infection by Coxsackie in 7% of the sample. In a second sample an enteroviral antigen (the VP-1 antigen) was found in 44/87 (51%), persisting in 39 (45%) at 4 months. None was detected in 20 normal controls, although others have found VP-1 antigen in 12% of randomly selected neurological patients (Halpin and Wessely, 1989), while Lynch and Seth (1989) reported equivalent levels of the antigen in CFS patients and depressed controls. The problems of sensitivity and specificity, and the apparent lack of relationship between symptoms and serology, means that the clinical relevance of such findings remains unclear (Wright, 1989).

Perhaps the most exciting possibilities come from new molecular biological techniques. Coxsackie B virus-specific probes have been used to demonstrate viral RNA sequences in the cardiac muscle biopsies of patients with cardiomyopathy (Bowles *et al.*, 1986). Archard *et al.* (1988) reported the results of similar techniques in a sample of muscle biopsies in cases of CFS provided by the Glasgow group. Virus-specific RNA could be detected in 25/96 (26%) of specimens. Four controls were negative, but none of 50 orthopedic specimens previously analyzed were positive. Thus, virus RNA can be demonstrated in a minority of these highly selected patients. Nevertheless, this result shows that the muscles of some patients

have been exposed to the virus, although the location of the virus-specific protein is yet to be determined. It does not show whether other tissues are similarly affected, when such exposure occurred (i.e., whether pre- or postmorbid), nor how this is related to the clinical syndrome.

Better clinical studies led to an increased skepticism about the importance of EBV in fatigue states. So far there is less information on the status of enteroviruses, but the realist must expect similar problems. It is already clear that, as in EBV, there is a dissociation between serological findings and clinical status (Calder *et al.*, 1987; Wilson *et al.*, 1989; Halpin and Wessely, 1989).

IMMUNE DYSFUNCTION

There has been a recent interest in possible immune dysfunction in CFS and its relationship to postviral states (Behan *et al.*, 1985; Lloyd *et al.*, 1988a). Straus (1988) has reviewed the immunological studies, and concluded that the findings are inconsistent and difficult to interpret. At present the only finding that has been both replicated and not disproved appears to be an increase in the levels of circulating immune complexes (Straus *et al.*, 1988; Yousef *et al.*, 1988). Most of the reasons for this unsatisfactory state of affairs have been covered in previous sections, in particular observer reliability, subject variability, normative data, and poor experimental design. Again, there is still no convincing evidence of a link between laboratory findings and clinical status, and some evidence to the contrary (Katon *et al*, 1988; Straus *et al.*, 1988).

There has been considerable interest in the role of interferon (IFN) in CFS, commencing with the clinical observation that exogenous IFN-α reproduced the neuropsychiatric features characteristic of CFS (MacDonald *et al.*, 1987), with a dose–response effect on performance measures (Smith *et al.*, 1988) Neither IFN-γ (Straus *et al.*, 1985; Jones *et al.*, 1985; Morte *et al.*, 1988; Lloyd *et al.*, 1988c) nor IFN-α (MacDonald, Burford, and Mann, personal communication) is elevated in CFS. Interest has shifted to the role of leukocyte 2′,5′-oligoadenylate synthetase, modestly increased in two series (Morag *et al.*, 1982; Straus *et al.*, 1985), which may indicate active suppression of IFN production.

Attention has also been given to interleukin 1 (IL-1). In animal studies it has been shown to activate T lymphocytes and induce fever by acting on the hypothalamus, leading to a decrease in REM sleep (Tobler *et al.*, 1984), and in the acute inflammatory response to be associated with changes in muscle metabolism (Baracos *et al.*, 1983; Dinarello, 1984), all of which is potentially relevant to CFS. There is an unpublished report of elevated IL-1β in 13/25 selected chronic fatigue patients (Behan, quoted in Dawson, 1989), although more modest elevations are known to occur in untrained normal men who overexert (Evans *et al.*, 1986). Given

that activated T lymphocytes produce IL-2 (Rubin *et al.*, 1985), and that increased serum IL-2 has been associated with both schizophrenia and brain damage (Ganguli and Rabin, 1989), one might predict that reports of elevated IL-2 in CFS will be forthcoming. In the meantime, others have found significant reductions in IL-2 in CFS patients (Kibler *et al.*, 1985; Katon *et al.*, 1988).

A further problem is the role of psychiatric illness as a potential confounder. Readers of this volume will be well aware that psychiatric disorder is associated with immune dysfunction, although both the relevance and specificity of the observed changes are unclear, and perhaps simplistic (King and Cooper, 1989). Since there is no doubt that immune dysfunction causes an increased risk of infection, it is possible that psychiatric illness is associated with an increased risk of both immune disorder and viral infection. Psychiatric illness (like physical inactivity) is a potential confounder of any proposed link between viruses and chronic fatigue, viruses and immune disorder, and immune disorder and chronic fatigue. Just as no researcher into a possible carcinogen would fail to record smoking habits, no researcher in this equally complex field should neglect to measure psychiatric disorder.

CFS AND PSYCHIATRY

Is There a Specific Fatigue Syndrome?

Before CFS, postviral fatigue, or its variants can be accepted as a diagnostic entity, it is necessary to show that it is not identical to known psychiatric disorders. Regrettably, some have chosen to overcome this problem by ignoring it, but recent evidence has shown this to be unacceptable.

There is surprisingly little evidence that a specific fatigue syndrome exists for anything other than a brief period of time after a known viral illness. Perhaps the most convincing evidence comes from the prospective studies of White (1989), who confirmed that a fatigue syndrome does exist after definite EBV infection, as distinct from depression. It was more frequent and lasted longer (mean duration 9 weeks compared to 3 weeks) than post-EBV depression. Barsky *et al.* (1988) studied upper-respiratory-tract infections using both self-report and objective measures, and concluded that the "relationship between objective assessed medical morbidity and patients' subjective experience was surprisingly weak. Medical morbidity did not emerge as an impressive correlate of symptomatology, discomfort and disability." Even in the immediate outcome of minor infection, depression as an independent variable was a weak but significant predictor of the number of days disabled.

Furthermore, these are only short-term studies. By the time most CFS

patients are seen in hospital, the mean duration already ranges from 18 months to 13 years (Buchwald *et al.*, 1987; Bell and Bell, 1988; Straus *et al.*, 1988; Wessely and Powell, 1989; Manu *et al.*, 1988a; Katon *et al.*, 1988).

Psychiatric Disorder and CFS

The principal associations of the complaint of chronic fatigue are the symptoms of depression and anxiety. This has been found in studies of the community (Chen, 1986), of students (Montgomery, 1983), and in primary care (Buchwald *et al.*, 1987; Kroenke *et al.*, 1988). The exact relationship between fatigue and psychiatric disorder (as opposed to psychiatric symptoms) has yet to be determined. However, there is strong evidence that most patients complaining of fatigue will have minor psychiatric morbidity, and that the rate of diagnosable psychiatric disorder increases with both the severity and duration of fatigue, as well as the number of accompanying symptoms (Goldberg and Huxley, 1980; Shepherd *et al.*, 1981; Clare and Blacker, 1986).

The only studies that utilize modern research diagnostic interviews in the evaluation of CFS have been conducted in the general hospital setting. There is now convincing evidence that the majority of CFS patients seen in hospital practice (which is where previous research has been based) satisfy criteria for psychiatric disorder. Manu *et al.* (1988a) screened 135 self-referrals to a special fatigue clinic in a university hospital: 67% had psychiatric diagnoses, 3% had medical diagnoses, 5% had operationally defined CFS, and 25% were unexplained. This suggests that further detailed screening of such patients for medical diagnoses has a low yield (Morrison, 1980; Havard, 1985; Hellinger *et al.*, 1988) and most continue to have medically unexplained fatigue.

There are now at least four studies of those referred by their physicians to hospital with chronic fatigue for which no medical explanation can be found. All studies report samples of patients with either physician or self diagnoses of CFS or its local equivalent. A Canadian group interviewed 24 patients with "neuromyasthenia" (Taerk *et al.*, 1987). Two thirds were current cases of major depression, while half had a history of affective disorder prior to the "fatiguing" illness. However, the research diagnostic criteria employed included fatigue as a symptom of psychiatric disorder, thus introducing an unwanted circularity into the results. Wessely and Powell (1989) studied 47 referrals to an English specialist neurology hospital with chronic unexplained fatigue, and found that 72% had a psychiatric diagnosis, using research diagnostic criteria modified to exclude fatigue. Two American studies gave similar figures (Katon *et al.*, 1988; Kruesi *et al.*, 1989). All reported that major depressive disorder was the commonest diagnosis, accounting for more than half of the sample, but it was not the only diagnosis, emphasizing the heterogeneity of CFS. In a separate small sample, Taerk and Abbey (1989) report

that over 80% of selected CFS patients had a first-degree relative with psychiatric illness.

Many will be surprised at these high rates of psychiatric disorder, especially since many seem to go unrecognized by the physician. One explanation is provided by Kruesi *et al.*, (1989), who noted the marked dissociation that occurred between the perception of physical and psychological symptoms in these patient groups. This is related to the importance of physical attributions in determining referral patterns and acceptance of treatment (Wessely, 1990a). Wessely and Powell (1989) matched cases of CFS with cases of major depression in a psychiatric hospital. There were no symptomatic differences between the groups, but profound differences emerged in the pattern of responses to questions concerning self-diagnosis and symptom attribution. Physical, as opposed to psychological, explanations of illness, almost invariably to a virus, were the principal reason for the marked differences in referral patterns.

Conclusion

It thus appears that the majority of CFS in hospital practice patients have recognizable psychiatric disorder. In 1904 Charles Dana proposed that neurasthenia was a heterogeneous condition, and many suffered from psychiatric illness, a view echoed in a recent editorial on CFS (Swartz, 1988). However, Dana concluded "I shall be very much disappointed if those who read this paper should flippantly express their interpretation of it by saying 'Well, he justs wants to make out that all neurasthenics are crazy people and ought to be locked up'." Such a warning is appropriate for a variety of reasons.

First, simply because many CFS patients satisfy criteria for affective disorder should not imply that the conditions are identical. In the context of neurasthenia and depression, Shweder (1988) has forcibly argued against this view, and in the social and clinical context it is true that the difference between depression and neurasthenia/CFS may be more important than the similarities (Wessely, 1990b). It is unclear whether such arguments are equally relevant to a discussion of the psychobiological basis of chronic fatigue.

Second, in all the studies reviewed, a minority of patients do not satisfy criteria for psychiatric illness. Such patients may have similar disorders to the majority, or may develop such disorders on follow-up, or alternatively may have a different nosological illness. At present, approximately a quarter of CFS patients encountered in hospital practice have no medical or psychiatric diagnosis.

Third, it is worth emphasizing (although perhaps not to the audience of this book) that psychiatric diagnoses are largely symptomatic descriptions, and convey relatively little information on etiology.

RISK FACTORS FOR CFS

Viral Illness

It has already been demonstrated that it is almost impossible to assess the role of viruses in the etiology of CFS from cross-sectional studies. Instead, valid information can only be gained from longitudinal studies of the outcome of known viral illnesses.

One of the few such studies concerns the outcome of serious enteroviral infections (Lepow *et al.*, 1962), in which 306 cases of aseptic meningitis were followed up. At 3 months, fatigue, poor concentration or motor disturbances (usually tightness or weakness) persisted in 32% of the original cohort, but this had reduced to 3% by 2 years, although there were neither controls nor complete follow-up. Muller *et al.* (1958) traced 238 cases of primary aseptic meningitis after between 2 and 12 years. No differences were found between cases and controls on measures of behavioral disturbance or mental health; instead, persistent morbidity was predicted by previous psychological disturbance.

A less favorable prognosis for the survivors of encephalitis is shown by a controlled 5-year follow-up of St. Louis encephalitis (Lawton *et al.*, 1970), a serious insect-borne arbovirus. Neurasthenic and affective symptoms were the most frequently observed sequelae, in particular exhaustion and fatigue, occurring in 35% of cases but only 9% of controls. Similarly, although the parkinsonian sequelae of encephalitis lethargica are well known, von Economo (1931) also described prolonged psychasthenic states with a "striking tendency to fatigue," identical to modern chronic fatigue syndromes. It can be concluded that viral illnesses do convey an increased risk of CFS, but so far this is related to their capacity to cause CNS damage, rather than persistent infection. Although there is a wealth of scientific studies concerning the mechanisms for persistent viral infection (Southern and Oldstone, 1986), such mechanisms have yet to be demonstrated in CFS, although recent speculation on viral persistence in the central nervous system and affective disorder raises exciting possibilities (Webb and Parsons, 1990).

Psychological Vulnerability and Past Psychiatric Illness

Prospective studies remain the best method of assessing the role of psychological vulnerability in the etiology of CFS. For obvious reasons such studies are rare. Nevertheless, a few exist. Six hundred people in employment were psychologically tested prior to the 1957 epidemic of Asian flu (Imboden *et al.*, 1961). All subjects were exposed to the epidemic. Serological surveillance established that those identified as psychologically vulnerable did not have an increased risk of infection, but having done so were ill for a longer period of time. The most common symptom in the "vulnerable group" was tiredness or weakness. Psychological vulnerability was a risk factor for duration of illness and fatigue, although the period of follow-up was short. The findings were replicated twice: first in a prospective study of the effects of immunization (Canter *et al.*, 1972), and later in an extraordinary study (Canter, 1972) in which volunteers were given tularemia. Not only did the "vulnerable" group report more symptoms, but the actual duration of fever was longer, which raises questions about the interaction between host and pathogen yet to be answered.

The less satisfactory alternative is to use the presence of past psychiatric history as a retrospective marker of psychological vulnerability. This is a reasonable strategy, as underascertainment is more likely than overascertainment, but it must be emphasized that it is still open to selection bias. It appears that between 40 and 60% of CFS patients seen in hospital practice have experienced previous episodes of psychiatric disorder before the commencement of their CFS (Taerk *et al.*, 1987; Katon *et al.*, 1988; Wessely and Powell, 1988; Kruesi *et al.*, 1989), with only one study giving discrepant results (Hickie *et al.*, 1990). This is particularly intriguing since two studies (Kruesi *et al.*, 1989; Katon *et al.*, 1988) looked at patients chosen on the basis of abnormal serology. This may be a result of selection bias and chance, or may again reflect a complex host–virus interaction that remains largely unexplored (Straus, 1988).

Multifactorial Models

It is becoming clear that neither an exclusively organic nor psychiatric model will explain the clinical picture of CFS. There are several conditions in which models have been developed that incorporate both organic and psychological factors, for example the outcome of minor head injury (Lishman, 1987) and chronic pain (Fordyce, 1976). Furthermore, such models also allow for different factors to have differing relevance over time. We have argued for a similar model in CFS (Wessely *et al.*, 1989; Wessely, 1990a), emphasizing the role of postmorbid variables, such as attributions, coping styles, inappropriate treatment, and the like. We have also argued that cognitive and behavioral explanations analogous to those advanced in chronic pain are relevant to CFS, and have described cycles of depression, misattribution, inactivity, and further fatigue as contributing to the persistence of CFS (Wessely *et al.*, 1989; Butler *et al.*, 1991). Only further work will tell how accurate such models are.

Some support comes from the preliminary findings of the studies of White (1989) previously mentioned. In a large cohort of patients followed up after developing primary EBV, the predictors of CFS differed with time. At 2 months, fatigue was associated with a decrease in IgG capsular antigen response, and also a decrease in IgM to viral capsular antigen. However, this was not the case at 6 months. Instead, fatigue at 6 months was predicted by psychiatric illness before the infective episode. The preliminary conclusion is that immune factors are associ-

ated with immediate fatigue, but past psychiatric history predisposes to fatigue states of longer duration. Such findings are also consistent with a model in which short- and long-term prognosis are influenced by very different factors. Further analysis of this important multidisciplinary study is awaited with interest.

At this stage it is impossible to quote reliable figures on the prognosis of CFS. Although all studies to date emphasize the poor prognosis, all are prevalent studies based on hospital samples, and thus will overestimate duration. Nevertheless, the general experience is conveyed by Behan and Behan (1988): "Most of the cases seen do not improve, give up their work and become permanent invalids." There is evidence of diagnostic stability over time (Macy and Allen, 1933–1934; Wheeler *et al.*, 1950), although, given the protean nature of fatigue, a small number will continue to develop more clear-cut neurological diagnoses during follow-up (Wessely and Thomas, 1990). A poor prognosis is also noted in primary care, and over 50% remain symptomatic at 1 year (Kroenke *et al.*, 1988; Nelson *et al.*, 1987). Finally, some have used evidence of poor outcome as proof of the neurological origin of CFS (Ramsay, 1986; Hyde and Bergmann, 1988). In fact, persistent morbidity does not serve to discriminate between psychiatric and neurological causes of fatigue.

However, all such conclusions remain tentative. Case definition is variable, follow-up rarely systematic, and samples unrepresentative. Those whose CFS is associated with affective disorder (a substantial number, if not the majority) may have a particularly poor prognosis, since not only is affective disorder of sufficient severity to lead to hospital associated with poor outcome (Lee and Murray, 1988), but persistence of somatic symptoms, especially fatigue, after 1 year of treatment for depression has been associated with persistence of affective disorder for 4 or more years (Cadoret *et al.*, 1980). Conversely, both the absence of somatic symptoms in general, and the absence of fatigue in particular, were associated with better outcome in a study of new psychiatric outpatients (Huxley and Goldberg, 1985). A fuller account of the prognosis of CFS is contained elsewhere (Wessely, 1990a).

THE EVIDENCE FOR "EPIDEMIC" FATIGUE

Although there remain often intense disagreements concerning the nature of sporadic CFS, such disputes seem almost like consensus in the light of the controversy surrounding epidemic forms of CFS. In both Britain and the United States, the appearance of epidemic variants of CFS has led to bitter argument. In Britain, controversy continues to surround the mysterious illness that swept through the staff of the Royal Free Hospital in 1955 (Medical Staff of the Royal Free Hospital, 1957), which is seen by some as mass hysteria (Mausner and Gezon, 1967; McEvedy and Beard, 1970), and by others as evidence of a new organic

illness named myalgic encephalomyelitis (Ramsay, 1986). Fortunately, such arguments need not concern us here, because the features of the illness do not correspond with modern definitions of CFS. Fatigue was not a prominent part of the picture: all agree the illness was contagious, while the symptoms were neurological or quasi-neurological depending upon one's interpretation. Most regrettably, the name "myalgic encephalomyelitis" has been attached to this epidemic phenomenon in addition to becoming the leading English synonym for CFS. This serves only to confuse the picture yet further (Byrne, 1988; Wessely and Thomas, 1990).

Different arguments surround a specific outbreak of CFS in the United States, the so-called "Lake Tahoe" epidemic. Reports (Peterson *et al.* 1986) of an outbreak of a fatiguing illness in this area of Nevada led to a rash of popular and scientific articles on a new mystery disease (Barnes, 1986), with intense speculation about a possible link to a new virus. Unlike the Royal Free outbreak, and related episodes, in which there was no doubt about the observed increase in morbidity (instead the controversy was whether the contagion was of emotional distress or infectious agent), at Lake Tahoe it is by no means certain that an epidemic occurred at all. Here the argument is not only the nature of the morbidity, but whether or not it represents an increase over normal rates.

The major problem lies in accurate knowledge of base rates, since time–space clustering can only be interpreted in the light of the distribution of CFS in the whole population. Such information is lacking. Nevertheless, various features suggest that no true increase in morbidity occurred. Cases were only being diagnosed in one practice, and other doctors in the area were not seeing anything unusual (Boly, 1987). In the "epidemic" a number of patients "with fatigue who would not otherwise have traveled to Incline Village for medical care had referred themselves specifically for EBV testing in 1985, thus creating an increase in cases in the area" (Holmes *et al.*, 1987). Part of the explanation may thus be a combination of altered medical perception, increased case finding, and a floating denominator. No transmissible agent has been identified, and the current consensus is against an infectious etiology (Schooley, 1988).

Both altered medical perception and a floating numerator have been noted before in less publicized outbreaks. In an earlier outbreak of "ME," May *et al.* (1980) demonstrated that an "epidemic" was the result of altered medical perception of the normal levels of illness found in an enclosed community, so that the increased case rate reflected an altered threshold rather than new morbidity. Both mechanisms explain another brief epidemic of an "infectious" disease, in which cases resulted from an unreliable laboratory test leading to overdiagnosis. Increased public awareness then led to the expected epidemic of "cases" (Mausner and Gezon, 1967). The role of the media in increasing public awareness of a "new" disease cannot be underestimated, nor can the role of doctors in creating new illnesses (Eisenberg, 1988).

WHY VIRUSES?

If the evidence implicating viruses in the etiology of CFS is less than conclusive, why have such labels as chronic EBV or postviral fatigue achieved such ready acceptance and widespread impact? The idea that viruses may substantially contribute to fatigue states has a long history (Arndi, 1892; Kraepelin, 1902; Savill, 1906). Indeed, faulty research first led to an intense, albeit unsuccessful, search for a fatigue vaccine in the years preceding the outbreak of World War I (Rabinbach, 1982).

The reasons lie in the intuitive appeal of viruses. In the community the commonest reason advanced to explain vague, unexplained symptoms is "a virus" (Pill and Stott, 1981). Such attributions are also on the increase, at the expense of earlier explanatory systems involving personal responsibility. Viruses are by definition external agents: "They originate outside the individual" (Helman, 1978). Helman goes on to write that "The germ has its own volition and cannot be directly controlled by the host. The victim of a germ infection is therefore blameless" (with the possible exception of sexually transmitted diseases).

This is an important concept in understanding CFS. Believing your illness is caused by a virus has many advantages. It lessens guilt and avoids blame. Patients who attribute somatically based symptoms to external causes may be less disturbed by them (Watts, 1982). CFS patients with affective disorder show less guilt but more self-esteem than matched depressed controls (Powell *et al.*, 1990). Finally, all those with clinical experience of CFS patients will recognize that many are firmly convinced of the physical, external origin of their symptoms and resistant to explanations involving psychological mechanisms.

Unfortunately, such attributions also have less desirable consequences. If you believe your symptoms are due to a virus, then it is impossible to exert any control over them, and recovery is left in "the lap of the gods." There is now evidence showing that in a number of diseases external attributions, and external locus of control, are associated with prolonged illness and impaired rehabilitation (Watts, 1982; Partridge and Johnson, 1989). Imboden *et al.* (1959) found that patients who attributed symptoms to "chronic brucellosis," a now-discredited diagnosis, were distinguished by a conviction of organic disease, a reluctance to discuss emotional issues and a preoccupation with somatic symptoms. One of the many factors contributing to the observed poor prognosis of CFS may be the nature of the disease attribution itself (Wessely, 1990a). Levi-Straus concluded that for a sick person to recover from any mysterious illness, it was necessary to have an explicit system of belief and explanation, whose accuracy was irrelevant. What cannot be accepted "are the incoherent and arbitrary pains, which are an alien element in her system." Recovery occurs once such symptoms are integrated within a meaningful system. However, "no such thing happens to our sick when the causes of their diseases have been explained to them in terms of secretions, germs or viruses" (Levi-Straus, 1963).

CONCLUSIONS

The balance between agent and host is important in any infectious disease. Logic suggests that in the condition of post-infectious fatigue, it is the host that may be as, if not more, important than the virus. In this context, one can do little better than repeat Pasteur's aphorism that "la germe c'est ne rien: c'est la terre qui est toute" (Laudenslager, 1987). There is a variety of evidence in favor of his intuition.

The viruses that are claimed to be responsible for fatigue are common. Exposure to EBV is nearly universal. Clinical infection with viruses such as influenza occurs in normal people several times a year, while subclinical infection is even commoner: it is worth repeating the assertion that the ratio of subclinical to clinical severe enterovirus infection is of the order of 1000:1 (Pallansch, 1988). CFS is not associated with a single specific pathogen, but has been reported after a number of infections, not all of them viral (Salit, 1985; Behan and Behan, 1988; Wessely and Powell, 1989). The alleged agents are not normally serious pathogens and although it is true that usually innocuous viruses may rarely cause severe illnesses, in such cases evidence of physical morbidity is easy to find, unlike in cases of chronic fatigue. Finally, many people have an identical clinical fatigue syndrome without apparent clinical exposure.

So far no evidence has been presented of clinical (as opposed to merely laboratory) reactivation or disease progression, despite the fact that many patients have an illness that may persist for decades. Lack of progression allied to the lack of development of frank neurological involvement disproves the occasional analogy with a slow virus infection (Sutton, 1978). On the contrary, George Beard (1880), the first person to describe CFS under the label of neurasthenia, asserted that it was actually associated with increased longevity!

Thus, conclusive evidence of a direct link between viruses and chronic fatigue remains elusive. It is unnecessary to insist on all of Koch's postulates being fulfilled before one accepts that such a link exists (Rivers, 1937), but one must insist on a more basic epidemiological principle: that the cause (viruses) must precede the effect (fatigue). The evidence of psychological vulnerability to CFS, and the role of psychiatric disorder as a possible confounder of the links between immune abnormalities and CFS, suggests that even this is not certain.

Finally, CFS itself appears to be a heterogeneous condition, and most, but not all, cases of CFS seen in general hospitals satisfy criteria for psychiatric illness. In patients with CFS, clinical status is associated more with psychological well-being than any laboratory measure.

WHAT SHOULD BE PRESENTED AT THE NEXT ICVO CONFERENCE?

Probably the greatest current problem in the field of CFS is the paucity of reliable epidemiological data. Currently both prevalence and case–control studies

are being initiated in primary care in Scotland, England, and the United States. Only a primary care, if not community based, study can overcome the problems of bias that effectively prevent further progress. The most sophisticated molecular virology will be of little use until previous methodological and epidemiological flaws are overcome.

The second major area for research lies in the role of effect modifiers. It is this author's belief that models involving a single agent and single disease will possess little explanatory power in anything other than a highly selected minority. Work is needed on factors that link agent and host, such as genetic, immunological, and psychosocial premorbid vulnerability, and postmorbid variables including cognitive, behavioral, and social factors. Such work should also concentrate on the change from acute to chronic illness, and from adaptive to maladaptive behaviors. Such an approach implies a dynamic, rather than a static, model of CFS.

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