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REVIEW

VIRUSES, NEUROSIS AND FATIGUE

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Abstract—The evidence for viral infections as a cause of anxiety, depression and fatigue is reviewed. It is argued that in order to fully understand any proposed relationship the effects of psychosocial factors on immunity, convalescence and illness behaviour must be acknowledged.

Keywords: Viruses, Fatigue, Neurosis, Psychoimmunology.

INTRODUCTION

Viral infections have been implicated in the aetiology of a variety of neurological and neuropsychiatric syndromes. In some instances the connection between the viral infection and subsequent neurological morbidity is clear, for example poliomyelitis. In herpes simplex encephalitis, direct damage to the temporal lobes may cause a variety of amnestic syndromes [1], as well as autism-like syndromes [2], Tourette-like syndromes [3, 4] and psychosis [5]. In 1931, von Economo [6] described a variety of sequelae to encephalitis lethargica, including Parkinsonism and psychosis, and since then the notion of postencephalitic Parkinson's syndrome has been widely accepted [7]. Other neurological diseases, for example Guillain-Barré syndrome and subacute sclerosing panencephalitis, are related to previous viral infections, although the causal mechanisms are poorly understood [8]. These syndromes have been extensively reviewed elsewhere and will not be considered further. Similarly, there has been growing interest in viral infections as a putative cause of schizophrenia, with recent contenders including prenatal exposure to influenza [9, 10] and adult exposure to Cytomegalovirus [11].

Research which aims to demonstrate a causal link between viral illness and subsequent psychiatric morbidity has a long and confusing history. During the past 100 yr, numerous claims have been made linking viral infections and subsequent psychiatric morbidity. Many of these have not stood the test of time. In this review we will therefore concentrate on the evidence for such an association, since we argue that this is the necessary first stage before one can turn to possible mechanisms.

Linking rare infective agents with rare but dramatic neurological diseases is relatively simple compared with the challenge facing researchers today for viral causes of psychiatric disorders. In a given year, 20–30% of a population will meet accepted criteria for psychiatric morbidity [12]. Similarly, fatigue is a common symptom affecting around 10% of the population at any point in time [13]. The viral

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illnesses which have been implicated as a cause of psychiatric syndromes are themselves commonly experienced and ubiquitous. In the United Kingdom most adults experience four symptomatic viral illnesses per year [14]. It would therefore be easy for an individual to attribute psychiatric symptoms to a viral infection when no such link exists. This artefact is more probable if reliance is placed on retrospective studies or if inappropriate control groups are used. Another difference between psychiatric and neurological illness is that psychiatric morbidity is harder to measure objectively compared to conditions such as subacute sclerosing panencephalitis, making case definition more difficult.

PSYCHOIMMUNOLOGY

An important potential confounder in any study which aims to demonstrate a link between viral illness and subsequent psychiatric morbidity is the effect psychiatric illness, stress and life events may have on the immune system. This problem was hinted at by Essen-Moller in 1956 [15]. In a survey of psychiatric morbidity in a population of 2500, he found 23 individuals who were suspected of having suffered from mental complications of infection. The majority of cases suffered from 'asthenic' states characterized by fatigue and depressive symptoms. If, on the other hand, an attempt was made to define those particularly prone to infection in the community, those suffering from asthenic symptoms were seen as particularly susceptible—thus, a potentially circular relationship between viral illness and mental symptoms exists.

More recently a growing body of literature [16–24] has suggested that stress and psychosocial vulnerability are important determinants of immune function, and although this work has not always led to consistent findings, the results are worthy of closer examination. The evidence for this comes from a variety of sources reviewed below.

ACUTE STRESS AND THE IMMUNE SYSTEM

Animal studies have demonstrated changes in markers of immune function in animals under stress. Mice who have recently been stressed through various mechanisms, including avoidance-learning tasks, isolation from other mice and exposure to cold water, are more likely to show signs of infection and weight loss when inoculated with viruses (including coxsackie B [25], encephalomyocarditis virus [26] and West Nile virus [27]) than those who have not been subjected to stress. Further, examination of internal organs demonstrated higher titres of the virus in the stressed mice [25, 27]. The possible mechanism for this reduced immunocompetence could be that acute stress lowers white cell counts in mice. This effect appears to be driven by the adrenals, in that stressed adrenalectomized mice show no such change in leucocyte counts [28]. These studies appear to conflict with work on monkeys, which demonstrated that monkeys who had been subjected to an avoidance learning paradigm were more likely to survive experimental inoculation with poliomyelitis than non-stressed animals, despite a fall in their lymphocyte count [29].

In vitro studies in humans have shown modulation of markers of immune function in association with a variety of stresses. Most compare markers of cell-mediated or humoral immunity in individuals experiencing periods of stress with either normal,

matched controls or the same individuals at another (presumably stress-free) time. In the majority of studies, stress appears to be associated with reductions in immune reactivity. In bereaved widows and widowers, for example, changes in immune function such as a suppression of mitogen-induced lymphocyte proliferation have been noted after the death of their spouses [30]. Although there is no fall in overall levels of lymphocytes, this may indicate a possible reduction in immune reactivity [30]. This result accords with the higher death rate noted following bereavement [31]. Other life events may lead to reduced natural killer cell activity and alterations of T lymphocyte populations, and these findings correlate with severity of depressive symptoms [32]. Another example is that recently released prisoners of war in Bosnia showed altered immune function with raised lymphocyte counts and reduced natural killer cells when compared with normal controls [33], although these changes could have several overlapping explanations—infectious disease, malnutrition and psychological distress.

If serious life events can lead to changes in immune function, are there analogous changes for minor stresses? It is noteworthy that some alterations of immune markers can be demonstrated in experimentally induced affective states in actors [34]. Many of the studies of stress and immunity have used normal student populations: medical students in their first week of clinical training (a time presumably associated with some stress) show increased anxiety scores and T helper lymphocytes when compared with second year students [35]. Dental students show lower levels of salivary IgA during examinations, an effect which may be modulated by personality factors [36]. This result was not replicated in medical students [37] who instead showed diminished levels of natural killer cells. Natural killer cells also appear to be increased in well adjusted students when rated on the Minnesota Multiphasic Personality Inventory (MMPI) [38]. Further, medical students who are seropositive for Epstein Barr virus show a lower transformation level (i.e. more virus is required to transform B cells– a sign that the immune system is less reactive) on the first day of their final examinations than 1 month before, or after the summer vacation [39]. Finally, humoral response to hepatitis B vaccine appears to be affected by stress, with high scorers on a range of stress indices 2 months post-vaccination showing lower antibodies at 7 months, indicating that stress may decrease the responsivity of the immune system [40].

In summary, there is some evidence to suggest that even comparatively minor stresses are associated with changes in immune function. Most of this evidence suggests that stress has a net effect of attenuating immune responses. The next step is to examine whether such a change matters in terms of susceptibility to infection.

STRESS AND INFECTION

The question of whether stress leads to an increased propensity to infection has been explored with *in vivo* research in humans, where a volunteer is exposed to an inoculum of virus. Objective evidence of infection was provided by the study of Cohen *et al.* [41], who demonstrated that when 394 volunteers were inoculated with cold viruses, those who had experienced recent stress were more likely to show evidence of infection and experience clinical colds than those who scored low for stress. A dose–response effect was noted and the effect held for four other experimental viruses. Other researchers have demonstrated similar results with increased infection

rates in those who had experienced recent life events [42, 43], an increased likelihood of clinical infection in certain personality types [41, 44] and higher than expected rates of low mood immediately preceding infection [43]. Further, one report has demonstrated that adolescents who had suffered from clinical influenza were more likely to have psychiatric symptoms than those who had not had the clinical illness but did have positive serological evidence of recent infection [45]. Hence, it may be that it is the clinical illness (i.e the experience of symptoms) rather than viral susceptibility which is most influenced by psychological variables.

Results from research examining the relationship between psychosocial variables and recurrence rates from genital and oral herpes simplex infections are less conclusive [46, 47]. There is a trend to a higher recurrence rate in those scoring higher on the General Health Questionnaire (GHQ) [48] and in those suffering higher levels of stress [49, 50]. There is limited evidence that psychosocial intervention may improve recurrence rates for genital herpes simplex infections [51]. Finally, one study has examined the effects of academic performance and motivation in cadets at a military training college and demonstrated that the combination of high motivation and poor performance was related to an increased infection rate from Epstein–Barr virus [52].

It is possible that patients under stress are more likely to fall ill with a viral infection and suffer more neurotic symptoms than non-stressed individuals. It is also probable that psychosocial factors may lead to a more severe viral illness following experimental exposure. This research is open to criticism because it is often unclear what aspect of psychosocial functioning is being measured (for example, stress, personality type and psychological symptoms are often confounded). The concept of stress itself has been criticised [53] for its unreliability and imprecision. Furthermore, not all studies use objective measures of infection, so the psychosocial variable may simply be a predictor of illness behaviour (see below). Nonetheless, Cohen *et al.* [41] prospective design overcomes many of these problems and gives intriguing results.

DEPRESSION AND IMMUNITY

Another explanation for an observed association between viral infection and psychiatric disorder is reverse causality. The best studied psychiatric disorder is depression and this section will focus on the immune changes of that illness. The literature is complex and what follows is a brief résumé: the interested reader is referred to Weisse [54] for a review. The area to attract most interest in the psychoimmunology of depression is mitogen-induced lymphocyte proliferation. In this paradigm, lymphocytes of depressed patients are exposed *in vitro* to one of a number of mitogens and their proliferative response measured and compared to that of matched controls. Several studies have demonstrated a reduced response in depressed patients [55–62]. The result has not always been replicated [63, 64] and may only reflect changes in subgroups of depressed patients—for example, the change may be absent in depressed outpatients [65]. Others [66, 67] have suggested that less severely ill depressed patients show the most marked changes.

The explanation most commonly offered for this apparent reduction in cell-mediated immunity is altered hypothalamic–pituitary–adrenal (HPA) axis function

in depression [68]. Cortisol is a potent immunosuppressant and the state of hypercortisolaemia in depression may be associated with immunosuppression. Maes *et al.* [62] claim that approximately 45% of the variance in mitogen-induced lymphocyte proliferation can be explained in terms of HPA overdrive as measured by non-suppression of the dexamethasone suppression test (DST). Unfortunately, two studies have failed to demonstrate a relationship between reduced lymphocyte proliferation and HPA function, such as failure of cortisol to suppress on the DST [59] and increased urinary cortisol levels [60], so the role of HPA axis function remains unclear.

A second area of interest in the psychoimmunology of depression is the finding of an absolute leucocytosis in some depressed patients [69, 70]. Maes *et al.* [70] have also demonstrated an increase in the proportions of mature to immature immune cells, and have suggested that there is a net immune activation in depression. These effects appear to depend on severity of depression—increasing severity of depression, as indicated by the shift towards psychotic/melancholic states, is associated with increasing evidence of immune changes and activation. The cause of this finding remains speculative.

Other immune changes in depression include the findings that natural killer cell numbers are reduced and their killing capacity is attenuated [71–73]. Lower neutrophil activity has been observed and this effect is reversed as the depression is treated [74]. Finally, there is weak evidence that humoral immunity may be affected by depression, one study showing that a subgroup of depressed inpatients had lower IgM [75]. On the other hand, humoral response to cholera vaccine was no different in depressed subjects compared with normal controls [76].

In summary, depression is associated with a bewildering variety of alterations in immune function. How these changes are translated *in vivo* remains uncertain. What is much clearer is that cross-sectional studies, which attempt to use immune markers of past viral infection in patients with a depressive illness as evidence of a causal relationship, must be interpreted with extreme caution. Results could be explained in at least two ways: suppression of lymphocyte activation may make a depressed patient more susceptible to infection. Alternatively, the immune activation described above may lead to a general, non-specific increase in antibody titres which could in turn be mistakenly interpreted as evidence of viral infection causing depression.

NEUROSIS AND ILLNESS BEHAVIOUR

It is possible that patients suffering from psychological distress are those most likely to present to their doctor with a viral infection which would be dismissed as trivial by better adjusted patients. Cluff *et al.* [77] demonstrated that the apparent attack rate for clinically evident infection with Asian influenza in the 1957 pandemic was increased almost three-fold in high scorers on the MMPI administered prospectively; this result related to clinically evident illness, not actual infection as demonstrated by a rise in antibody titres. Other studies have shown similar effects on those scoring high on the Beck Depression Inventory [78] and measures of life events [79]. Viral illnesses are common and few patients will present to their doctors with symptoms. Given that psychiatric disorder is a major determinant of the decision to attend a doctor's surgery with many complaints, it is inevitable that individuals

with more neurotic symptoms are over-represented in cohorts of patients with viral illness recruited from primary care. There are several possible mechanisms for this: first it could reflect abnormal illness behaviour by which the patients present to a doctor with minor ailments because of their perceived distress. Secondly, it may be that patients with psychological disorder or subject to stress are vulnerable to experience and report more symptoms [80], because the psychiatric illness is associated with both somatic symptoms and a tendency to somatize, which may affect the patient's response to both the psychiatric disorder and the viral infection. Finally, it may be that patients with neurotic complaints are more prone than others to closely self-monitor for symptoms, and thus be more sensitive to, and likely to report, any bodily sensation.

NEUROSIS AND CONVALESCENCE

There is some evidence for the notion that personality factors will affect the duration of an illness and affect convalescence. One retrospective study [81] demonstrated higher scores on the MMPI in subjects who had prolonged illness with infectious mononucleosis and suggested that these subjects had lower 'ego strength' (as calculated from high scores on several subtests of the MMPI). A prospective study on sufferers from influenza demonstrated that those who were symptomatic (usually with fatigue, cough and insomnia) over 6 weeks after the initial illness were higher scorers on the Cornell Medical Index Health Questionnaire and the MMPI 6 months earlier than those who recovered quickly [82, 83]. Similar results were found in patients admitted to military hospitals with a range of acute respiratory infections [84]. Frank [85], examining the effects of an unknown infection (later found to be schistosomiasis) in American soldiers, concluded that their symptomatic recovery depended more on their faith in the doctors attending them than the illness itself. Similarly, perceived duration of upper respiratory infections may depend largely on the degree of support and stress the patient is subject to. Whether these findings represent differences in the immune system due to different personalities, or simply differences in illness behaviour, remains unclear.

The research reviewed so far indicates that psychosocial factors may affect illness behaviour (leading to more ready presentation to doctors with viral illnesses and a more prolonged convalescence). It is also probable (perhaps through the mediation of the humoral stress response) that psychosocial morbidity increases the risk and severity of infection.

POSTVIRAL DEPRESSION, ANXIETY AND FATIGUE

This section reviews evidence linking psychiatric morbidity after viral illness. Three methodological strategies have been used. First come early descriptive studies which have reported psychiatric illness in patients who have had a known viral illness. These studies usually gave no estimate of psychiatric morbidity in the general population and failed to use standardized assessments of symptoms. The second group of studies have attempted to demonstrate evidence of past or present viral illness in people suffering from a known disorder. Most such studies have been applied to the study of chronic fatigue syndrome (CFS). As there is a well-established

link between CFS and psychiatric illness (see below), it is reasonable to interpret any link between CFS and viral illness as an example of viral illness causing psychiatric morbidity. These studies follow a case control design. The third group of studies follow a longitudinal design and follow-up patients after a well documented viral infection. These studies are capable of detecting not only syndromes but also symptoms as measured on standardized rating scales such as the General Health Questionnaire. As in any cohort study, they are also capable of establishing the nature of the precipitating infection at onset, instead of depending on retrospective serological techniques after the onset of the psychiatric disorder.

Research has focused on a wide variety of different viruses. In the following section evidence from early descriptive studies will be briefly considered. Then two specific viruses, Epstein Barr Virus (EBV) and Coxsackie B virus (CBV), will be considered as they have been the focus of most research. CBV will be reviewed in the context of recent interest, suggesting it to be a cause of CFS.

EARLY STUDIES

The association of influenza with depression has long been recognized. Kraepelin [86] identified 11 cases of apparent postinfluenzal depression following the 1890–92 epidemic. In 1895, Espagnol [87] emphasized the mild and transient nature of the depression which was seen in most cases. Nonetheless, Menninger [88], writing in 1921, mentions the 1890–1892 influenza epidemic and remarks that: 'It is conceivable that this, through a general loss of mutual confidence, optimism, and faith, brought about the financial panic of 1893, and (the recent epidemic of 1919) may in part be responsible for the general unrest of the present moment generally ascribed to the late war alone.' Reporting his own large series of cases he concluded that although a transient lowering of mood was commonly experienced following influenza, more serious mental illness was uncommon and tended to be associated with a clear-cut encephalopathy.

Hepatitis A represents another viral infection recognized to be associated with psychiatric morbidity [89]. In 1944, Caravati [90] reported a number of soldiers who complained of fatigue, right upper quadrant discomfort, fat intolerance and emotional instability following clinically resolved hepatitis A infections. Two further reports suggested that the condition (which had only been reported in soldiers) was psychosomatic. The basis for this was normal physical and laboratory examinations [91]. Although no formal psychiatric examination was performed, these reports suggested the syndrome was similar to 'effort syndrome' (a fatigue state described in soldiers) and concluded that the illness led to premorbid neurotic traits being unmasked. Similar conclusions were reported [92] from a group of soldiers who failed to recover from postvaccinial (yellow fever) hepatitis. There is no recent English language literature on 'posthepatitis' syndrome to the authors' knowledge.

The Herpes Virus family are of particular interest, being neurotropic and because they may lie quiescent following initial infection. There is conflicting evidence for a relationship between herpes simplex virus and depression: whist some studies have shown higher titres amongst depressed patients than in the general population [93] or other psychiatric patients [94], these results have not been replicated [95]. Several studies have sought to find markers of Epstein–Barr Virus (EBV) infection in the

sera of depressed patients. Despite some reports of depression following from EBV infection [96–98], larger studies with control groups have found no effect [99, 100].

Another viral infection to have been suggested as a cause of depression is Borna Disease virus. Evidence of infection was found in 12 of 265 subjects with depression, but in none of the 105 controls [101]. These results have been replicated by the same group [102], who found that patients suffering from affective disorder were 2–3 times more likely to have antibodies to the Borna virus than normal controls. These results must be interpreted cautiously in the light of the immune changes seen in depression (see above). It is possible, for example, that there is a generalized immune activation which causes a non-specific increase in antibody titres to a range of different viruses. An example of how this could happen is provided by Holmes *et al.* [103], who looked at immune markers of viral infection in chronic fatigue syndrome and found raised antibodies to several different viruses simultaneously in many of their patients.

CHRONIC FATIGUE SYNDROME

Another possible link between viral infections and psychiatric morbidity is via the chronic fatigue syndrome (CFS), sometimes known as myalgic encephalomyelitis (ME). As another synonym for the condition, postviral fatigue syndrome, suggests, these conditions are often thought to be sequelae of viral infections. This clinical link with infection has a long and distinguished history, starting with the observation that influenza was a frequent precursor of neurasthenia, the original chronic fatigue syndrome [104].

The link with psychiatric disorder and CFS is well established. Psychiatric symptoms such as depression and anxiety are present in most subjects seen with the label of ME or CFS [105, 106]. The clinician who has the largest such practice in the U.K. has written that depression is almost invariable [107]. Others have stated that, in severe cases, depression and CFS are indistinguishable [108]. Given that other symptoms, such as fatigue, anorexia, sleep disturbance, poor libido, poor memory and concentration dominate the clinical picture, it is not surprising that the majority of cases seen in either specialist care [109–113] or primary care [114] fulfil criteria for psychiatric disorder, well in excess of what might be expected as a 'reaction' to physical illness [109, 115, 116].

If the association between psychiatric disorder and CFS is well established, is there evidence that CFS is caused by viral infections? The main thrust of the argument for a viral cause of CFS comes from the anecdotal histories patients give [105, 109, 117]. Up to 90% of patients with CFS from infectious disease clinics will identify an initial, presumably viral, illness at onset [118]. There are obvious problems with relying on these accounts. First, there is a temptation in any illness to 'search after meaning' and retrospectively relate onset to a coincidental event. This effect is all the more probable in the case of CFS because most patients prefer a viral as opposed to a psychological explanation for their symptoms, as this seems to protect against guilt, avoids the stigma of psychological disorder and preserves self-esteem [119]. In our culture, viruses (apart from Human Immunodeficiency Virus, HIV) are disease explanations free from personal culpability. Secondly, selection bias is a powerful effect in these studies: patients have been referred to the infectious disease clinic often *because* of the history of infectious illness.

In the United States, the debate has centred on the possibility that EBV could cause a syndrome of persistent malaise and fatigue—'chronic EBV syndrome'. In one group of patients there is a clear-cut disease characterized by end organ damage, pancytopenia and grossly abnormal EBV serology [120]. These patients have a high incidence of lymphoproliferative malignancy and mortality is high. Other studies reported prolonged somatic symptoms in patients which—because they included fatigue, poor concentration, subjective reports of fever and sore throats—were reminiscent of glandular fever [121–125]. When laboratory investigations revealed possible markers for EBV, the term 'chronic mononucleosis' was introduced, and a link with EBV persistence assumed. There has been increasing doubt over the reliability of such research. First, EBV infection is common and many asymptomatic people continue to have raised antibodies following an acute infection [126]. A second problem relates to the use of unreliable laboratory procedures [127]. Third, the retrospective design of most of these studies led to a powerful ascertainment bias—individuals who had suffered from recent EBV were more likely to be referred [128].

In one prospective study, Lambore *et al.* [129] found an excess of cases of somnolence, fatigue and depression in students suffering from EBV infectious mononucleosis compared with those who had suffered other respiratory infections, and this excess persisted for over 1 yr in 6% of cases. White *et al.* [130] in another prospective study have followed up 250 patients presenting to primary care with either upper respiratory tract infections (URTI) or EBV infectious mononucleosis. They found that there was indeed an excess of fatigue in the EBV group, both at 2 and 6 months postinfection. The fatigue at 2 months was predicted by the severity of the acute illness. At 6 months, fatigue was predicted by premorbid psychosocial factors such as introspection, life events and past psychiatric history, as well as physical fitness at 2 months follow-up, implying that it is these factors, rather than the viral infection itself, which are responsible for the persistent fatigue seen in some patients.

In Great Britain, the preoccupation of many researchers has been to establish a link between enteroviral infections and CFS. A number of early reports [131–134] suggested that patients who have postviral fatigue syndrome (which was not defined in these series) show evidence of recent infection with CBV as defined by higher incidence of CBV antibodies, first IgG and later IgM. The first group of studies used IgG as evidence of past infection. This was replaced by IgM, a better marker for recent infection. The initial results in each case were promising, suggesting higher levels of exposure in the CFS cases than in controls. Unfortunately, these studies were open to criticism because of ascertainment bias and inadequate case definition. Better studies, particularly that of Miller *et al.* [135], showed equal serological evidence of previous infection between fatigued cases and normal controls.

However, medical technology came to the rescue. Apart from serological evidence, there are other means of demonstrating CBV infection in patients with CFS. For example, Yousef *et al.* [136] were able to demonstrate enterovirus particles in the stools of five of 76 patients with CFS which persisted for 1 yr. Further, a group-specific enteroviral antigen (VP-1) was demonstrated in approximately one half of their cases, with none detected in normal controls. The controls were family members and were thus not randomly selected. Indeed, they were selected because they were

neither fatigued nor suffering from a viral illness—hence this 'control' group have no estimate of the random or community prevalence of the factors under study. Other studies have been able to demonstrate the antigen in 12% of randomly selected neurological patients [137] and equivalent levels have been found in patients with CFS and depressed controls [138]. The test has now been withdrawn.

Yet again technology provided the answer—the polymerase chain reaction technique (PCR) has been used to detect virus-specific RNA in the muscles of 26% of cases with CFS, whilst controls were all negative [139]. Unfortunately, using more sophisticated technology does not overcome the previously mentioned problems of selection and ascertainment bias, and it is not surprising to learn that in the most recent study from the same group, no differences were noted in the proportion of positive biopsies between CFS cases and controls with a variety of other muscle diseases [140].

If there was a direct link between enteroviral infections and the onset of CFS, viral meningitis would be a suitable disease to study because case definition is clear, the disease is often caused by enterovirus and the illness affects the CNS. Reports of epidemics [141–143] emphasize the benign nature of the illness, although few such reports have attempted a systematic follow up. In infants there may be a lowering of IQ at follow up [144]. Children may show decreased concentration, fatigue and headaches when followed up over 2–10 yr [145]. One study demonstrated one third of sufferers from echo virus meningitis complained of headaches 1 month following the illness [146]. A further study demonstrated significant morbidity (primarily headache, dizziness and mental fatigue) 3–4 yr following viral meningitis in 22 patients followed up, and this morbidity was associated with more severe forms of the illness [147]. Two larger studies [148, 149] have followed patients with viral meningitis. Lepow *et al.* [148] showed an increase in morbidity 3 months postinfection, with around two thirds of patients complaining of fatigue, headache, clumsiness or paraesthesias. Their follow up was incomplete but the impression was of complete recovery in the vast majority by 1 yr. Muller *et al.* [149], who traced 238 cases of aseptic meningitis and followed them up over 2–12 yr, could detect no difference between their mental health and that of normal normal controls.

Perhaps the effect is not specific for enteroviruses but is related to CNS trauma of any kind. This is suggested by the only follow-up study we have been able to locate of the longer term outcome of encephalitis in adults. Those who survived St Louis Encephalitis were three times more likely to report neurasthenic symptoms than normal controls [150]. In children it is certainly the case that encephalitis may affect psychosocial functioning to a severe degree [151].

Human Herpes Virus 6 (HHV-6) has some similarities with EBV, not least having been implicated as a possible cause of CFS. As with EBV and CBV, early studies [152, 153] reported an association between CFS and raised titres of antibodies to HHV-6. Unfortunately, the virus is common and antibodies to it are almost universal within the adult population. Other cross-sectional studies have failed to replicate the finding [154, 155].

Similarly, Human T cell Lymphotrophic virus (HTLV-II) was identified in the U.S.A. as a possible cause of CFS on the basis of a series of six adult and child cases of CFS recruited from diverse sources [156]. This report caused a flurry of

media attention. As before, a series of studies have failed to replicate the finding [157].

CONCLUSIONS

The previous section demonstrates many of the difficulties with the research into possible viral causes of CFS. The difficulties of ascertainment bias and retrospective design are vital—meaningful results are unlikely to be obtained from case control studies. The advantages of a longitudinal design are amply demonstrated by White *et al.* [130] careful follow up of EBV infections which allow the interaction of psychosocial and disease factors to be properly examined.

Unfortunately, it is difficult to perform a truly prospective study of viral infections and their effects on mental health. The work of Cohen *et al.* [41] points to the possible confounding effects of psychological and social factors on immune status. The work of Cluff *et al.* [77] demonstrates a further confounder—that of personality affecting illness behaviour.

Taken as a whole, the evidence that viral infections cause depression or chronic fatigue is weak. It is probable that whilst infection may contribute to the onset of CFS it is only likely to do so in predisposed individuals. Otherwise, there has been a singular failure to identify a single causative organism for CFS.

The interactions between infection, immunity, stress, mental illness and social factors provide a complex illustration of the subtle interface between psyche and soma and must be acknowledged before drawing conclusions from research attempting to demonstrate direct causality between viral illness and psychiatric morbidity.

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