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EDITORIAL

Chronic fatigue syndrome – mapping the interior[1]

Over a century ago Beard referred to fatigue as the 'Central Africa of medicine – an unexplored territory which few men enter' (Beard, 1869). The last decade has seen major advances in our understanding of chronic fatigue syndrome (CFS). Much is now known of the epidemiology, clinical features and prognosis of the condition (Wessely *et al.* 1998), and a number of recent papers have reported randomized trials of successful treatments involving cognitive behaviour therapy (CBT) and graded exercise (Sharpe *et al.* 1996; Wearden *et al.* 1996; Deale *et al.* 1997; Fulcher & White, 1997). Despite these advances, which have defined some of the broad landmarks of the illness, and improved the care of patients, many areas remain uncharted. Several papers published in this issue of *Psychological Medicine* take us into such unexplored territory.

Capuron *et al.*'s contribution (pp. 291–297) does not directly address CFS, but will be of interest to most researchers in the field. CFS is frequently attributed to viral illness, and although trivial viral infections are not associated with later chronic fatigue (Wessely *et al.* 1995), the picture is different with severe infections, such as glandular fever, viral meningitis and hepatitis A (Berelowitz *et al.* 1995; White *et al.* 1995; Hotopf *et al.* 1996) with cohort studies demonstrating clear associations. Surprisingly little is known of the acute psychological effects of viral illness – the topic of Capuron *et al.*'s paper. Using a battery of neuropsychological tests, the authors found that subjects experiencing influenza-like symptoms, performed less well than controls on specific memory tasks – an effect which was unrelated to pyrexia. These deficits – the authors argue – may be due to the role of cytokines released during infection. Although cytokines were not measured in this study, recent work on acute influenza suggests that acute symptoms correlate best with levels of circulating interleukin (IL)-6 (Hayden *et al.* 1998). Cytokine receptors exist in a variety of brain structures, and may modulate the hypothalamic–pituitary–adrenal axis (HPA) (McEwen *et al.* 1997), which has in turn been implicated in the pathogenesis of CFS, leading some researchers to argue for a central role of cytokines in CFS (Ur *et al.* 1992; Hickie & Lloyd, 1995). Such speculation is, of course, a long way from determining a causal pathway between infection and CFS, but suggests that integrative studies assessing the role of immune, neuroendocrine and behavioural factors following viral infection (and other stressors associated with fatigue) might be a useful approach to understanding the condition (Bennett *et al.* 1998).

Among the cardinal features of CFS is the fact that exertion – be it mental or physical – worsens fatigue. Sufferers are frequently avoidant of exertion, and such avoidance is associated with a poorer outcome (Sharpe *et al.* 1992; Joyce *et al.* 1997). It is worth asking why CFS patients avoid, and a number of dynamic studies that observe changes in symptoms or psychomotor function in the context of exertion begin to explain better why this may happen. CFS patients do not show any evidence of peripheral muscular problems (Wessely *et al.* 1998), but they do report more symptoms and show more marked changes in cognitive function following exercise than healthy controls (Blackwood *et al.* 1998; LaManca *et al.* 1988). The study by Smith *et al.* (pp. 283–290) demonstrates a similar picture with CFS patients developing fatigue more rapidly than healthy controls when asked to perform tasks that involved prolonged attention. These findings were not specific to CFS – they occur in sleep deprivation, and sleep disorder is common in CFS.

What does this mean in terms of treatment? Randomized controlled trials show that treatments that aim to overcome fear of exertion have useful benefits in CFS – graded exercise treatment and

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CBT both do this. Deale *et al.*'s (1997) study of CBT demonstrated that the fear that exertion would lead to lasting damage was the most important attribution to address in CBT – more important than addressing the often contentious issue of aetiology. It is important to remember that the belief that exertion will cause a worsening is founded on real experiences of sufferers, thus behavioural change requires a leap of faith on the part of the patient.

The genetics of fatigue and CFS has been largely ignored, unless one counts previous work showing a high familial loading for neurocirculatory asthenia (Cohen *et al.* 1951). Given the difficulty of defining the phenotype, it is probably more sensible to start with the genetics of the principal symptom, fatigue, and three studies in this issue add substantially to our knowledge of this neglected issue. In this issue Farmer *et al.* (pp. 279–282) explored the issue in a twin study of children; they have derived a model where up to 76% of the variance of fatigue could be explained by genetic factors. Hickie *et al.*'s studies (pp. 259–277) assessed the heritability of fatigue in mid to late life, and again found a strong heritable component, although they do not report estimates of heritability.

The interpretation of additive models which aim to distribute observed variance into mutually exclusive genetic and environmental categories is problematical (Rothman & Greenland, 1998). The relative contribution of heritable and environmental risk factors to the variance of a disorder in populations is not fixed. Most conditions are likely to involve gene–environment interactions, and heritability depends critically on the prevalence of environmental risk factors. Paradoxically, the more prevalent such risk factors are, the more genetic the condition will appear to be. This point was made intuitively by the epidemiologist Geoffrey Rose (personal communication), who remarked that in a population where everybody smoked, lung cancer would appear to be a genetic disorder. Allison & Faith (1997) demonstrated the point formally in a model where the increasing prevalence of environmental risk factors was associated with an increase in the heritability of the condition under study (in this case obesity). Thus, we believe that the fashion for heritability fractions must be tempered with caution – the fraction is a limited parameter that applies only to the specific population under study.

The strength of the Australian paper (Hickie *et al.* 1998*a*) is to go further and explore shared and unique risk factors for fatigue, depression, psychological distress, and anxiety. This approach has proved fruitful in improving understanding of the overlap between anxiety and depression (Kendler *et al.* 1992). The association between fatigue and common psychiatric disorders has always been controversial. There is no question that the association exists, with patients with CFS experiencing approximately twice as much psychiatric disorder as controls with medical illness. However, there are a number of important differences between CFS and depression. Exploring the neurobiology of these conditions has thrown up interesting leads – such as the relative underactivity of the HPA axis in fatigue as opposed to the opposite overactivity of the axis in depression (Demitrack *et al.* 1991; Cleare *et al.* 1995). Hickie's paper demonstrates that depression, anxiety, psychological distress and fatigue are probably determined by different underlying genetic factors, with one uniquely contributing to fatigue. Similarly, they identified a single environmental factor that appears to be unique to fatigue. From these findings they argued that psychiatric classification should include prolonged fatigue states.

A number of caveats have to be applied to these studies – the first of their kind to address the genetics of chronic fatigue. The complex models shown in Hickie *et al.*'s papers are derived by a process of induction. They have managed partly to replicate the same model in two samples; however, the results require further replication before the authors' suggestion that the classification of psychiatric disorders is changed. Farmer *et al.*'s study used parental reporting of fatigue among the twins; however parents and their children often disagree about the presence of symptoms (Taylor *et al.* 1996). The results may also be due to parents of identical twins seeing them as more similar than do parents of dizygotic twins. Finally, the Australian study relied on twins aged over 50 years, whereas most patients seen and treated for CFS are considerably younger. Their finding of unique heritable and environmental components of fatigue in this sample may be due to confounding by physical illness. Physical illness – commoner in older samples – is strongly associ-

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ated with fatigue, and is likely to have genetic and environmental determinants entirely independent of depression and anxiety. Thus, considerable caution must be taken before generalizing this study, and it is premature to use this as evidence to justify a change in psychiatric nosology.

Studies into the immunology of CFS give a confused and contradictory picture. The final genetic study (Hickie *et al.* 1998*b*) attempted to separate out the possible contributing factors to psychological distress, fatigue and immune responsiveness. There is a wealth of evidence that stress affects immune functioning (McEwen *et al.* 1997). Using a small sample of twins, Hickie *et al.* proposed a model by which the same genes coding for psychological distress and fatigue are also implicated in immune responsiveness but that most of the variability in immune responsiveness could be attributed to environmental factors which were unrelated to psychological distress and fatigue. The finding that stress and immune responsiveness are related via a common genetic mechanism has the potential to greatly simplify psychoneuroimmunology and such integrative approaches are welcome in a field which requires links to be made between symptoms and objective markers of immune activity.

Where should CFS research go from here? There is a clear need to follow up the lead given by the genetic studies. The model, which suggests separate genetic factors predict fatigue as opposed to depression and anxiety, may be important to psychiatric taxonomy, and has implications for the minority of patients with CFS without psychiatric disorder. Furthermore, it may provide clues as to biological markers of susceptibility to CFS, and lead eventually to assessing the role of specific candidate genes for the condition.

There is an increasing need for integrative research into CFS. If anything is clear, it is that CFS cannot be understood via a single mechanism. Given that most research still takes place in patients who have been ill with CFS for many months or years, it is usually impossible to determine whether the biological and psychological changes, which have been reported in sufferers, are primary or secondary. The relative role of immune changes, viral infections, HPA axis underactivity, behavioural change, and attributional style may be best explored using prospective cohort studies of conditions, which are known to be associated with later fatigue states. Such conditions might include stressful life events, viral infection or post-operative states.

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