

# Chronic fatigue syndrome: an update focusing on phenomenology and pathophysiology

Hyong Jin Cho<sup>a</sup>, Anna Skowera<sup>b</sup>, Anthony Cleare<sup>a</sup> and Simon Wessely<sup>a</sup>

## Purpose of review

Chronic fatigue syndrome is a controversial condition especially concerning its clinical definition and aetiopathogenesis. Most recent research progress has been made in phenomenology and pathophysiology and we focused our review on these two areas.

## Recent findings

The phenomenology research supports the notion of a discrete fatigue syndrome which can be distinguished from depression and anxiety. The current case definition, however, may need an improvement based on empirical data. Recent advances in understanding the pathophysiology of chronic fatigue syndrome continue to demonstrate the involvement of the central nervous system. Hyperserotonergic state and hypoactivity of the hypothalamic–pituitary–adrenal axis constitute other findings, but the question of whether these alterations are a cause or consequence of chronic fatigue syndrome still remains unanswered. Immune system involvement in the pathogenesis seems certain but the findings on the specific mechanisms are still inconsistent. Genetic studies provide some evidence of the syndrome being a partly genetic condition, but environmental effects seem to be still predominant and identification of specific genes is still at a very early stage.

## Summary

The recent findings suggest that further research is needed in improving the current case definition; investigating overlaps and boundaries among various functional somatic syndromes; answering the question of whether the pathophysiologic findings are a cause or consequence; and elucidating the involvement of the central nervous system, immune system and genetic factors.

## Keywords

chronic fatigue syndrome, pathophysiology, phenomenology

## Abbreviations

<b>ACTH</b>	adrenocorticotrophic hormone
<b>CBT</b>	cognitive–behavioural therapy
<b>CFS</b>	chronic fatigue syndrome
<b>CNS</b>	central nervous system
<b>FSS</b>	functional somatic syndrome
<b>HPA</b>	hypothalamic–pituitary–adrenal

© 2006 Lippincott Williams & Wilkins  
0951-7367

## Introduction

Chronic fatigue syndrome (CFS) is best understood as one of the medically unexplained or functional somatic syndromes, meaning that there are currently no disease-specific, demonstrable abnormalities of structure that satisfactorily explain ill health [1]. Functional somatic syndromes (FSSs) include irritable bowel syndrome, fibromyalgia, CFS, multiple chemical sensitivity, chronic pelvic pain, temporomandibular joint dysfunction, and more recently Gulf War illness. These conditions overlap in their symptoms, causes and treatment. It has been argued that these similarities outweigh differences between them, or, if there are differences between the syndromes, the fault lines are not yet apparent [2]. On the other hand, there are also arguments in favour of considering these symptom-defined conditions separately, and unless and until more research emerges outlining distinct pathophysiological processes between the different syndromes, it is unlikely that this debate can be resolved [3••]. A third view on the issue would be the following: the relationship between CFS and other FSSs is analogous to the one between depression and anxiety, that is, they are mostly dealt with as distinct clinical entities but the existence of a mixed form is also recognized. A few recent studies reviewed in this article support this alternative idea, but the current body of evidence may, at the most, generate this hypothesis.

Given this brief overview on functional somatic syndromes, the context in which CFS is situated, the present paper reviewed original research on CFS published during 2004 and the first semester of 2005. We focused the review on the phenomenology and pathophysiology of CFS, the two areas in which most progress has been made. *Medline* was searched from January 2004 to June 2005 with the search strategy adopted in a previous systematic review: containing ‘chronic fatigue syndrome’, its 17 synonyms and ‘fibromyalgia’ as key words [4•].

Curr Opin Psychiatry 19:67–73. © 2006 Lippincott Williams & Wilkins.

<sup>a</sup>Department of Psychological Medicine, Institute of Psychiatry and <sup>b</sup>Department of Immunobiology, Guy's, King's and St Thomas' School of Medicine, King's College London, London, UK

Correspondence to Dr Hyong Jin Cho, Department of Psychological Medicine, Institute of Psychiatry, King's College London, PO 62, Weston Education Centre, 10 Cutcombe Road, London SE5 9RJ, UK  
Tel: +44 20 7848 5417; fax: +44 20 7848 5408; e-mail: h.cho@iop.kcl.ac.uk

Current Opinion in Psychiatry 2006, 19:67–73

## Phenomenology

Recent research continues to support the nosological status of a fatigue syndrome that can in part be distinguished from anxiety and depression, albeit with strong associations, replicating early studies from UK and Australia [5,6] and work on the closely related neurasthenia construct [7]. Thus a discrete fatigue syndrome containing these symptoms was present among 5% of 150 American primary care patients 6 months after the onset of infectious mononucleosis [8<sup>•</sup>], replicating a previous British study [9]. Principal component analyses consistently delineated two fatigue factors at 2 and 6 months and one fatigue factor at 4 years. These factors were separate from a mixed anxiety and depressive factor.

In the latter studies [8<sup>•</sup>,9] fatigue syndrome was assessed prospectively after an identified trigger, namely Epstein–Barr virus (EBV). In clinical practice the situation is different, however, and clinicians are far more likely to encounter heterogeneity. Hence two new studies [10,11<sup>•</sup>] both confirmed heterogeneity in study populations defined by the 1994 CFS case definition [12]. Nisenbaum *et al.* [10] studied the community survey data from Wichita, Kansas, including 1391 chronically fatigued subjects (575 prolonged fatigue, 1085 chronic fatigue, 263 CFS-like and 43 CFS patients) using factor analyses to identify symptom dimensions of fatigue and cluster analyses to assign subjects to subgroups. Distributions of factor scores substantially overlapped across CFS subjects and non-CFS subjects. Three clusters identified also showed overlap between CFS and non-CFS subjects. This means that the 1994 CFS case-defining symptoms do not define a single clinical entity and there is a substantial overlap between CFS symptoms and symptoms of other unexplained chronic illnesses. Kennedy *et al.* [11<sup>•</sup>] compared three groups of patients, all of whom fulfilled the 1994 CFS case definition but self-reported different causes such as ‘ME’ ( $n = 48$ ), short for myalgic encephalomyelitis, a term popular with British patients more than doctors, ‘Gulf War syndrome’ ( $n = 24$ ) and self-reported exposure to organophosphate insecticides ( $n = 25$ ). Although all of them met the 1994 CFS case definition, significant differences in simple clinical measures and outcome measures were observed between groups. The authors concluded that the specificity of the CFS case definition should be improved to define more homogeneous groups of patients for the purpose of treatment and research. Using the data from the Wichita population-based survey, Solomon and Reeves [13] showed that, among 90 subjects with confirmed CFS, those with the following characteristics were more likely to have been previously diagnosed as having CFS: middle income (rather than higher income), sudden fatigue onset, complaint of tender lymph nodes and a sore throat. The study suggested that CFS patients reporting sudden fatigue onset, tender lymph nodes or a sore throat are

overrepresented in clinic-based samples and again supported the notion of heterogeneity in the population defined by the CDC-1994 criteria.

A population study using a national sample from the Swedish Twin Registry provided some evidence to explain this apparent paradox between the existence of a discrete fatigue syndrome and the heterogeneity of CFS population [14<sup>••</sup>]. The authors assessed those subjects who endorsed fatigue and possessed no exclusionary condition, imposing no current case definition but using a relatively unbiased classification strategy (four definitions differing in terms of duration, impairment and presence of CDC-1994 ancillary symptoms). Latent class analysis identified a class of individuals that strongly resembles clinical samples of CFS along with four other classes. On the other hand, using graphical methods and regression models, they asserted that the CDC-1994 criteria do not function well: there was no empirical support for the requirement of ‘four’ of the eight ancillary symptoms; the eight symptoms were not equivalent in their capacity to predict fatigue; and no combination of symptoms was markedly more heritable. In summary, despite the heterogeneity of chronic fatiguing illness observed, a discrete CFS-like entity seems to ‘exist’ only partially overlapping with major depression and chronic widespread pain, but the current case definition fails to identify it.

## Pathophysiology

We reviewed here the involvement of central nervous system (CNS), serotonergic system, hypothalamic–pituitary–adrenal (HPA) axis, immune system, genetics and psychological factors.

### Altered central nervous system

Neuroimaging studies revealed some structural and functional alterations of CNS among CFS patients. Two separate cohorts of CFS patients showed a marked decline in grey matter volume, compared with matched healthy controls, and this reduction was associated with the objectively measured decline in physical activity [15]. Subjective cognitive impairment, more specifically information-processing dysfunction, among CFS patients was linked to the objective findings by functional magnetic resonance imaging (fMRI) which correspond to an increased neural resource allocation [16]. Another fMRI study [17<sup>•</sup>] suggested that CFS might be associated with dysfunctional motor planning. Two neurophysiologic studies also showed altered CNS functioning during motor activities with muscle contraction [18,19].

A series of twin studies from the same group revealed, however, that CFS patients were not different from their healthy twins concerning the above-mentioned and other previously thought to be key components of CFS:

neuropsychological dysfunction [20], regional cerebral blood flow [21], sleep [22<sup>•</sup>,23,24], immune system [25], markers of viral infection [26] and neurally mediated hypotension [27]. For example, the information-processing speed and efficiency in CFS patients were reduced when compared with healthy non-related controls but similar when compared with their healthy twins [20]; CFS twins reported significantly more subjective sleepiness than their healthy twins, but the objective measures were similar between them [22<sup>•</sup>]. These twin studies, which employ a matched-pair comparison that adjusts for many genetic and environmental factors not generally considered in traditional case-control, challenge several previous findings of CFS research, suggesting they may not be specific or pathogenetic for CFS.

On balance, recent evidence continues to develop the theme of a central as opposed to peripheral pathophysiology for CFS, even though some of the findings have been questioned and the specific mechanisms remain elusive as indeed they do for many related disorders.

#### **Serotonergic system**

Most of the existing evidence has suggested a hyperserotonergic state or upregulated serotonin receptors among CFS patients, in contrast to the hyposerotonergic state seen in major depression, although this has mainly been indirect evidence from neuroendocrine challenge studies. Two published studies have now measured directly the status of cerebral serotonin receptors in CFS. In the first, Cleare *et al.* [28<sup>•</sup>] showed decreased 5-HT<sub>1A</sub> receptor binding throughout the brain using positron emission tomography (PET), the reduction being most marked in the hippocampi bilaterally. The authors noted that it is possible that 5-HT<sub>1A</sub> receptor downregulation is a response to increased levels of synaptic serotonin, but also noted alternative explanations. For example, although Cleare *et al.* studied only non-depressed CFS patients, patients who do have depression show downregulation of 5-HT<sub>1A</sub> receptors even after treatment; since many CFS sufferers (including most of those studied by Cleare *et al.*) have a past history of depression, this is one possible explanation. Similarly, the effect on the serotonin system of the behavioural consequences of CFS (such as sleep disturbance and inactivity) remains unclear. In a second PET study in non-depressed CFS subjects, this time of the density of cerebral serotonin transporters, Yamamoto *et al.* [29] found reduced receptor binding in the rostral anterior cingulate of CFS patients and found that this correlated inversely with the level of reported pain (i.e. lower binding was related to higher pain scores) but not to other symptoms. These authors also point out that the reduced serotonin reported could be secondary to increased serotonin synaptic levels, or to changes in blood flow or neuronal density in these areas.

#### **Hypothalamic-pituitary-adrenal axis abnormalities**

Some of the most robust findings concerning the pathophysiology of CFS have been related to the HPA axis, with much evidence supporting mild HPA axis hypoactivity (reviewed by Cleare [30]). Recently published studies have provided further support for disruption to the HPA axis. Two studies have plugged a longstanding gap in the literature, that of regular blood sampling of adrenocorticotrophic hormone (ACTH) and cortisol throughout an entire 24-h circadian period. Both studies found underactivity of the HPA axis in the early morning in CFS, apparent in ACTH levels in one study and cortisol levels in the other [31,32<sup>•</sup>]. Further support that the HPA axis is underresponsive to direct stimulus came from two papers, one measuring the cortisol response to awakening and the other the ACTH response to hypoglycaemia, the latter study also finding a correlation with symptom duration and severity [33,34]. Although, as is typical in this literature, another study failed to find a blunted HPA axis response to challenge [35], these papers maintain the balance that the large majority of studies report a blunted HPA axis in CFS. Nevertheless, the key question still remaining unanswered is whether these alterations are a cause of CFS or a response to the behavioural changes typical of CFS (discussed by Cleare [36<sup>•</sup>]). The finding that HPA axis changes are more pronounced the longer CFS has been present [34] supports the latter assertion. Furthermore, two prospective studies of groups at high risk of developing chronic fatigue (post-EBV infection and post-surgery) found that the development of fatigue 6 months after was not associated with any HPA axis changes [37,38<sup>•</sup>]. One study however suggested the opposite, showing that a subset of healthy regular exercisers after being experimentally deprived of exercise for 1 week developed pain and fatigue, and these individuals had lower HPA axis function at the baseline of the experiment [39<sup>•</sup>]. In other words, a subset of healthy individuals in the general population may have altered HPA axis function, which might subsequently render them vulnerable to developing fatigue. Most of these studies have studied broadly defined sub-acute or chronic fatigue, and larger cohorts are required to clarify this issue with regard to the onset of more strictly defined CFS. A final complication to the area arises from the finding of Crofford *et al.* [32<sup>•</sup>] that there were subtle but opposite changes in the HPA axis between patients with CFS, fibromyalgia, or the combination. Notably, whereas cortisol levels were lowered in CFS, they were raised in fibromyalgia and normal in patients who met criteria for both CFS and fibromyalgia. The possibility that some HPA axis changes may be 'cancelled out' in the presence of both pain and fatigue is intriguing, not least because it offers another explanation as to why there have been inconsistencies between different studies that may not have characterized their samples sufficiently well.

### Immune dysfunction

CFS has been associated with changes in the immune system, especially with immune activation and perturbation in T and natural killer cell count and functions. Cytokines, major cell products reflecting immune cell function, were also suggested to play a role in the pathogenesis and clinical manifestation of CFS. Many studies measured various cytokines, mainly concentrating on pro-inflammatory ones such as TNF- $\alpha$ , IL-1 and IL-6 as these are known to be involved in the regulation of the HPA and sympathetic nervous system [40], but the results were contradictory [41–43].

A recent study [44<sup>\*</sup>] demonstrated diminished levels of mRNA and protein production for TGF $\beta$ 1 in CFS subjects when compared with healthy controls [44<sup>\*</sup>]. TGF $\beta$ 1, as a major regulatory cytokine, is involved in suppressing the immune system especially via inhibition of antibody production. Deficiency of TGF $\beta$ 1 in CFS subjects may contribute to symptoms such as myalgia and muscular fatigue. It is possible that TGF $\beta$ 1 could be an indicator of treatment response in CFS, but other studies that fail to find any differences in TGF $\beta$ 1 level in CFS patients suggest caution [45].

A recent proposal explored for CFS is the Th1/Th2 paradigm of immune-mediated diseases. One of the main supporting arguments is the frequent reporting of natural killer cell activity reduction in CFS [46–48]. Natural killer cells play a key role in the generation of Th1 type antiviral responses. Loss of their activity could result in a Th2 bias, persistent viral activation and finally chronic infection. More direct evidence of potential Th2 bias was reported in two studies: one showed an increased level of IL-4 mRNA which was associated with a CFS-like syndrome in Gulf War veterans [49]; and the other, using the intracellular cytokine staining method, showed an effector memory cell bias towards Th2-type responsiveness in CFS patients [50<sup>\*</sup>].

Another argument supporting the involvement of the immune system in the pathogenesis of CFS is the communication between the HPA axis and immune system via glucocorticoids. They can modulate immune responses by inhibiting the production of pro-inflammatory cytokines, therefore promoting the switch from Th1-type towards Th2-type responses, which is in agreement with the study by Skowera *et al.* [50<sup>\*</sup>]. Several studies investigated immune responses during and after stress as it is well known that stress and exercise can substantially exacerbate fatigue in CFS patients [51]. One report suggested an enhanced sensitivity of circulating leucocytes to increasing doses of dexamethasone in CFS patients undergoing a standardized psychosocial stress paradigm [52]. Recently, the same group examined the direct influence of stress (glucocorticoids) on the immune

system (lipopolysaccharide-induced pro-inflammatory cytokines production) in CFS patients [53<sup>\*</sup>]. Interestingly, they found that lipopolysaccharide-stimulated cytokine production decreases shortly after stress in CFS subjects, while it increases in controls.

Despite the wealth of immune data generated on CFS, caution is needed in interpreting them, as a systematic review on the issue previously showed [54], and future work should take into account other important contributing factors such as neuroendocrine, anatomic and genetic factors.

### Genetics

Genetic studies on CFS are not many to date, but there is some evidence of CFS being a moderately heritable condition from several twin studies [55–57]. A twin study using a Swedish national sample recently provided data broadly consistent with the previous studies demonstrating modest genetic effects and the clear importance of individual-specific environmental effects [58<sup>\*</sup>]. A distinctive point raised by this study, however, was that no definition of fatiguing illness (ranging from any fatigue to CFS-like illness) was more ‘genetic’ than another. Several studies on gene expression in peripheral blood mononuclear cells presented some apparently interesting findings indicating several genes as possibly involved in the pathogenesis of CFS, and captured much attention from the public [59<sup>\*</sup>,60]. A more recent study, however, reported no indication of differential expression between patient and control groups [61<sup>\*</sup>]. Taking into consideration all these studies and the fact that they performed a genetic scanning without an a priori hypothesis using a relatively small sample, any conclusions drawn at the present point seem premature and, certainly, further studies are required for a more accurate evaluation. Finally, two association studies, which are by definition performed with an a priori hypothesis for selecting candidate genes usually according to the current knowledge of the disease pathogenesis, reported the involvement of the serotonin transporter gene and the angiotensin-converting enzyme gene, the latter being associated with muscle metabolism and physical endurance [62,63]. Theoretically, in order to detect realistically small genotypic relative risks, large samples are required: thousands of cases and thousands of controls. Hence, again, these findings should be replicated further ideally by large association studies with correct candidate genes.

### Psychological aspects

Recent studies confirmed the importance of several psychological factors especially in maintaining CFS: lack of sense of control over symptoms [64], symptom focusing [65<sup>\*</sup>] and a physical attribution for fatigue [64,66].

## Treatment

An updated review on the treatment of CFS as a whole is available [67\*\*], and there are separately updated reviews on some interventions for CFS available in the Cochrane Library [68\*\*]. Hence we are reviewing here only some interesting points of the treatment which shed some light on the nature of CFS. Kop *et al.* [69] conducted a 5-day programme of ambulatory monitoring of physical activity and symptoms of fibromyalgia and CFS patients compared with controls, an objective and direct observation which provided more accurate and detailed information than self-reporting, the procedure usually adopted in other studies. Pain and fatigue were associated with reduced subsequent ambulatory activity levels, whereas activity levels were not predictive of subsequent symptoms. Thus, high-level activities may not necessarily lead to an increase in symptoms and this is one more piece of evidence to encourage patients to be engaged in exercise programmes. In accordance with this finding, the randomized controlled trial by Wallman *et al.* [70\*] demonstrated that graded exercise was associated with improvements in physical work capacity, as well as in specific psychological and cognitive variables.

Cognitive-behavioural therapy (CBT) has been shown to be effective so far but only in studies that use skilled therapists. In contrast a previous study [71] found that primary care doctors were unable to treat CFS effectively using CBT. Huibers *et al.* [72\*] tested CBT delivered by general practitioners to treat unexplained, persistent fatigue among employees and reported disappointing results. In two primary care studies, CBT was as effective as either counselling [73] or graded exercise therapy [74]. The absence of any control condition, however, limits the conclusions that can be drawn about absolute efficacy of either intervention.

## Conclusion

The present paper described recent findings on CFS in the light of the previous findings especially concerning phenomenology and pathophysiology. The studies on phenomenology seem to support the notion of a discrete fatigue syndrome which can be distinguished from depression and anxiety. The current case definition of CFS does not, however, seem to define a single clinical entity and may need an improvement based on empirical data. We have seen further advances in understanding the pathophysiology of CFS, centring on the CNS, which, because of the co-existence of physical and mental fatigability in the CFS construct, should remain the focus of attention. Dysfunction of the serotonergic system and abnormalities of the HPA axis are the most robust findings concerning the pathophysiology, and the overall evidence suggests hyperserotonergic state and hypoactivity of the HPA axis. Nevertheless, the question of whether these alterations are a cause or consequence of

CFS still remains unanswered. Immune system involvement in the pathogenesis of CFS is reflected via abnormal cytokine productions, perturbation of natural killer cells, and indication of Th2-type responses. Genetic studies on CFS, which are still scarce, provide some evidence of CFS being a partly genetic condition, but environmental effects seem to be still predominant and identification of specific genes is still at a very early stage. Finally, as mentioned in the introduction, a couple of recent studies could relate to the alternative hypothesis regarding the relationship between CFS and the other FSSs, that is, they are mostly dealt with as distinct clinical entities but the existence of a mixed form is also recognized. Sullivan *et al.* [14\*\*] suggested a possible distinction of CFS-like illness from chronic widespread pain with only partial overlap and Crofford *et al.* [32\*] found opposite changes in the HPA axis between CFS and fibromyalgia patients and an intermediate state in patients with both conditions. These recent findings suggest that further research is needed on the improvement of the current case definition of CFS; the investigation of the overlaps and boundaries among various FSSs; the involvement of CNS; the question of whether the pathophysiologic findings are the cause or consequence of CFS; and the high quality investigation of immune dysfunction and genetic contribution.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 119–120).

- 1 Barsky AJ, Borus JF. Functional somatic syndromes. *Ann Intern Med* 1999; 130:910–921.
- 2 Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? *Lancet* 1999; 354:936–939.
- 3 Wessely S, White PD. There is only one functional somatic syndrome. *Br J Psychiatry* 2004; 185:95–96.
- The authors conduct a debate on the cases for and against the proposition expressed in the title and summarize its key points.
- 4 Cho HJ, Hotopf M, Wessely S. The placebo response in the treatment of chronic fatigue syndrome: a systematic review and meta-analysis. *Psychosom Med* 2005; 67:301–313.
- This is a meta-analysis of a previously unexplored issue of CFS, the placebo response.
- 5 van der Linden G, Chalder T, Hickie I, *et al.* Fatigue and psychiatric disorder: different or the same? *Psychol Med* 1999; 29:863–868.
- 6 Hickie I, Koschera A, Hadzi Pavlovic D, *et al.* The temporal stability and co-morbidity of prolonged fatigue: a longitudinal study in primary care. *Psychol Med* 1999; 29:855–861.
- 7 Hickie I, Hadzi Pavlovic D, Ricci C. Reviving the diagnosis of neurasthenia. *Psychol Med* 1997; 27:989–994.
- 8 White PD, Thomas JM, Sullivan PF, Buchwald D. The nosology of sub-acute and chronic fatigue syndromes that follow infectious mononucleosis. *Psychol Med* 2004; 34:499–507.
- This was a prospective study in American primary care supporting the notion of a discrete fatigue syndrome.
- 9 White PD, Thomas JM, Amess J, *et al.* Incidence, risk and prognosis of acute and chronic fatigue syndromes and psychiatric disorders after glandular fever. *Br J Psychiatry* 1998; 173:475–481.
- 10 Nisenbaum R, Reyes M, Unger ER, Reeves WC. Factor analysis of symptoms among subjects with unexplained chronic fatigue: what can we learn about chronic fatigue syndrome? *J Psychosom Res* 2004; 56:171–178.

- 11 Kennedy G, Abbot NC, Spence V, *et al.* The specificity of the CDC-1994 criteria for chronic fatigue syndrome: comparison of health status in three groups of patients who fulfill the criteria. *Ann Epidemiol* 2004; 14:95–100. This study with empirical data called into question the specificity of CDC-1994 criteria.
- 12 Fukuda K, Straus SE, Hickie I, *et al.* The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med* 1994; 121:953–959.
- 13 Solomon L, Reeves WC. Factors influencing the diagnosis of chronic fatigue syndrome. *Arch Intern Med* 2004; 164:2241–2245.
- 14 Sullivan PF, Pedersen NL, Jacks A, Evengard B. Chronic fatigue in a population sample: definitions and heterogeneity. *Psychol Med* 2005; 35:1337–1348. This paper presents the interesting results of a population study using the Swedish Twin Registry on the nosology and heterogeneity of CFS and a critique on CDC-1994 criteria.
- 15 de Lange FP, Kalkman JS, Bleijenberg G, *et al.* Gray matter volume reduction in the chronic fatigue syndrome. *Neuroimage* 2005; 26:777–781.
- 16 Lange G, Steffener TJ, Cook DB, *et al.* Objective evidence of cognitive complaints in Chronic Fatigue Syndrome: A BOLD fMRI study of verbal working memory. *Neuroimage* 2005; 26:513–524.
- 17 de Lange FP, Kalkman JS, Bleijenberg G, *et al.* Neural correlates of the chronic fatigue syndrome: an fMRI study. *Brain* 2004; 127:1948–1957. This neuroimaging study showed the involvement of CNS on the pathophysiology of CFS.
- 18 Siemionow V, Fang Y, Calabrese L, *et al.* Altered central nervous system signal during motor performance in chronic fatigue syndrome. *Clin Neurophysiol* 2004; 115:2372–2381.
- 19 Schillings ML, Kalkman JS, van der Werf SP, *et al.* Diminished central activation during maximal voluntary contraction in chronic fatigue syndrome. *Clin Neurophysiol* 2004; 115:2518–2524.
- 20 Mahurin RK, Claypoole KH, Goldberg JH, *et al.* Cognitive processing in monozygotic twins discordant for chronic fatigue syndrome. *Neuropsychology* 2004; 18:232–239.
- 21 Lewis DH, Mayberg HS, Fischer ME, *et al.* Monozygotic twins discordant for chronic fatigue syndrome: regional cerebral blood flow spect. *Radiology* 2001; 219:766–773.
- 22 Watson NF, Jacobsen C, Goldberg J, *et al.* Subjective and objective sleepiness in monozygotic twins discordant for chronic fatigue syndrome. *Sleep* 2004; 27:973–977. This twin study investigates the specificity of sleep disturbance on the pathogenesis of CFS.
- 23 Watson NF, Kapur V, Arguelles LM, *et al.* Comparison of subjective and objective measures of insomnia in monozygotic twins discordant for chronic fatigue syndrome. *Sleep* 2003; 26:324–328.
- 24 Ball N, Buchwald DS, Schmidt D, *et al.* Monozygotic twins discordant for chronic fatigue syndrome: objective measures of sleep. *J Psychosom Res* 2004; 56:207–212.
- 25 Sabath DE, Barcy S, Koelle DM, *et al.* Cellular immunity in monozygotic twins discordant for chronic fatigue syndrome. *J Infect Dis* 2002; 185: 828–832.
- 26 Koelle DM, Barcy S, Huang ML, *et al.* Markers of viral infection in monozygotic twins discordant for chronic fatigue syndrome [see comment]. *Clin Infect Dis* 2002; 35:518–525.
- 27 Poole J, Herrell R, Ashton S, Goldberg J, Buchwald D. Results of isoproterenol tilt table testing in monozygotic twins discordant for chronic fatigue syndrome. *Arch Intern Med* 2000; 160:3461–3468.
- 28 Cleare AJ, Messa C, Rabiner EA, Grasby PM. Brain 5-HT<sub>1A</sub> receptor binding in chronic fatigue syndrome measured using positron emission tomography and [<sup>11</sup>C]WAY-100635. *Biol Psychiatry* 2005; 57:239–246. This neuroimaging study directly investigated the serotonergic system in CFS.
- 29 Yamamoto S, Ouchi Y, Onoe H, *et al.* Reduction of serotonin transporters of patients with chronic fatigue syndrome. *Neuroreport* 2004; 15:2571–2574.
- 30 Cleare AJ. The neuroendocrinology of chronic fatigue syndrome. *Endocr Rev* 2003; 24:236–252.
- 31 Di Giorgio A, Hudson M, Jerjes W, Cleare AJ. 24-Hour pituitary and adrenal hormone profiles in chronic fatigue syndrome. *Psychosom Med* 2005; 67:433–440.
- 32 Crofford LJ, Young EA, Engleberg NC, *et al.* Basal circadian and pulsatile ACTH and cortisol secretion in patients with fibromyalgia and/or chronic fatigue syndrome. *Brain Behav Immun* 2004; 18:314–325. This study measured ACTH and cortisol throughout a 24-h circadian period comparatively among patients with CFS, fibromyalgia or both conditions.
- 33 Roberts AD, Wessely S, Chalder T, *et al.* Salivary cortisol response to awakening in chronic fatigue syndrome. *Br J Psychiatry* 2004; 184:136–141.
- 34 Gaab J, Engert V, Heitz V, *et al.* Associations between neuroendocrine responses to the Insulin Tolerance Test and patient characteristics in chronic fatigue syndrome. *J Psychosom Res* 2004; 56:419–424.
- 35 Inder WJ, Prickett TC, Mulder RT. Normal opioid tone and hypothalamic-pituitary-adrenal axis function in chronic fatigue syndrome despite marked functional impairment. *Clin Endocrinol (Oxf)* 2005; 62:343–348.
- 36 Cleare AJ. The HPA axis and the genesis of chronic fatigue syndrome. *Trends Endocrinol Metab* 2004; 15:55–59. This is a review on the involvement of the HPA axis in CFS.
- 37 Candy B, Chalder T, Cleare AJ, *et al.* Predictors of fatigue following the onset of infectious mononucleosis. *Psychol Med* 2002; 33:847–855.
- 38 Rubin GJ, Hotopf M, Papadopoulos A, Cleare A. Salivary cortisol as a predictor of postoperative fatigue. *Psychosom Med* 2005; 67:441–447. This was a prospective study trying to answer the question of whether the HPA axis alteration is a cause or consequence of CFS.
- 39 Glass JM, Lyden AK, Petzke F, *et al.* The effect of brief exercise cessation on pain, fatigue, and mood symptom development in healthy, fit individuals. *J Psychosom Res* 2004; 57:391–398. This experimental study with healthy individuals tried to answer the question of whether the HPA axis alteration is a cause or consequence of CFS.
- 40 Kishimoto T, Akira S, Narazaki M, Taga T. Interleukin-6 family of cytokines and gp130. *Blood* 1995; 86:1243–1254.
- 41 Amel Kashipaz MR, Swinden D, Todd I, Powell RJ. Normal production of inflammatory cytokines in chronic fatigue and fibromyalgia syndromes determined by intracellular cytokine staining in short-term cultured blood mononuclear cells. *Clin Exp Immunol* 2003; 132:360–365.
- 42 Cannon JG, Angel JB, Ball RW, *et al.* Acute phase responses and cytokine secretion in chronic fatigue syndrome. *J Clin Immunol* 1999; 19: 414–421.
- 43 Swanink CM, Vercoulen JH, Galama JM, *et al.* Lymphocyte subsets, apoptosis, and cytokines in patients with chronic fatigue syndrome. *J Infect Dis* 1996; 173:460–463.
- 44 Tomoda A, Joudoi T, Raab E, *et al.* Cytokine production and modulation: Comparison of patients with chronic fatigue syndrome and normal controls. *Psychiatry Res* 2005; 134:101–104. This immune study reported the involvement of TGFβ-101 with CFS.
- 45 MacDonald KL, Osterholm MT, LeDell KH, *et al.* A case-control study to assess possible triggers and cofactors in chronic fatigue syndrome. *Am J Med* 1996; 100:548–554.
- 46 Klimas NG, Salvato FR, Morgan R, Fletcher MA. Immunologic abnormalities in chronic fatigue syndrome. *J Clin Microbiol* 1990; 28:1403–1410.
- 47 Tirelli U, Marotta G, Improta S, Pinto A. Immunological abnormalities in patients with chronic fatigue syndrome. *Scand J Immunol* 1994; 40:601–608.
- 48 Caligiuri M, Murray C, Buchwald D, *et al.* Phenotypic and functional deficiency of natural killer cells in patients with chronic fatigue syndrome. *J Immunol* 1987; 139:3306–3313.
- 49 Hanson SJ, Gause W, Natelson B. Detection of immunologically significant factors for chronic fatigue syndrome using neural-network classifiers. *Clin Diagn Lab Immunol* 2001; 8:658–662.
- 50 Skowera A, Cleare A, Blair D, *et al.* High levels of type 2 cytokine-producing cells in chronic fatigue syndrome. *Clin Exp Immunol* 2004; 135:294–302. This study investigated the Th1/Th2 paradigm in CFS.
- 51 Wood GC, Bentall RP, Gopfert M, *et al.* The differential response of chronic fatigue, neurotic and muscular dystrophy patients to experimental psychological stress. *Psychol Med* 1994; 24:357–364.
- 52 Gaab J, Rohleder N, Heitz V, *et al.* Enhanced glucocorticoid sensitivity in patients with chronic fatigue syndrome. *Acta Neuropsychiatr* 2003; 15:184–191.
- 53 Gaab J, Rohleder N, Heitz V, Engert V, Schad T, Schurmeyer TH, Ehlerl U. Stress-induced changes in LPS-induced pro-inflammatory cytokine production in chronic fatigue syndrome. *Psychoneuroendocrinology* 2005; 30:188–198. The authors examined the relationship between the HPA axis and immune system via glucocorticoids.
- 54 Lyall M, Peakman M, Wessely S. A systematic review and critical evaluation of the immunology of chronic fatigue syndrome. *J Psychosom Res* 2003; 55:79–90.
- 55 Hickie I, Kirk K, Martin N. Unique genetic and environmental determinants of prolonged fatigue: a twin study. *Psychol Med* 1999; 29:259–268.

- 56** Buchwald D, Herrell R, Ashton S, *et al.* A twin study of chronic fatigue. *Psychosom Med* 2001; 63:936–943.
- 57** Farmer A, Scourfield J, Martin N, *et al.* Is disabling fatigue in childhood influenced by genes? *Psychol Med* 1999; 29:279–282.
- 58** Sullivan PF, Evengard B, Jacks A, Pedersen NL. Twin analyses of chronic fatigue in a Swedish national sample. *Psychol Med* 2005; 35:1327–1336. This describes the most recently published twin study of CFS using the Swedish Twin Registry.
- 59** Kaushik N, Fear D, Richards SCM, *et al.* Gene expression in peripheral blood mononuclear cells from patients with chronic fatigue syndrome. *J Clin Pathol* 2005; 58:826–832.  
This was a gene expression study with positive findings which captured much public attention.
- 60** Powell R, Ren J, Lewith G, *et al.* Identification of novel expressed sequences, up-regulated in the leucocytes of chronic fatigue syndrome patients. *Clin Exp Allergy* 2003; 33:1450–1456.
- 61** Grans H, Nilsson P, Evengard B. Gene expression profiling in the chronic fatigue syndrome. *J Intern Med* 2005; 258:388–390.  
This negative study was published a couple of months after the study by Kaushik *et al.* [59\*].
- 62** Narita M, Nishigami N, Narita N, *et al.* Association between serotonin transporter gene polymorphism and chronic fatigue syndrome. *Biochem Biophys Res Commun* 2003; 311:264–266.
- 63** Vladutiu GD, Natelson BH. Association of medically unexplained fatigue with ACE insertion/deletion polymorphism in Gulf War veterans. *Muscle Nerve* 2004; 30:38–43.
- 64** Huibers MJ, Bleijenberg G, van Amelsvoort LG, *et al.* Predictors of outcome in fatigued employees on sick leave: results from a randomised trial. *J Psychosom Res* 2004; 57:443–449.
- 65** Moss-Morris R, Sharon C, Tobin R, Baldi JC. A randomized controlled graded exercise trial for chronic fatigue syndrome: outcomes and mechanisms of change. *J Health Psychol* 2005; 10:245–259.  
This paper describes, in addition to the results of the trial, possible mechanisms of clinical improvement.
- 66** Huibers MJ, Bultmann U, Kasl SV, *et al.* Predicting the two-year course of unexplained fatigue and the onset of long-term sickness absence in fatigued employees: results from the Maastricht Cohort Study. *J Occup Environ Med* 2004; 46:1041–1047.
- 67** Reid S, Chalder T, Cleare A, *et al.* Chronic fatigue syndrome. *Clinical Evidence* 2005. Available at <http://www.clinicalevidence.com/ceweb/conditionpdf/1101.pdf> [Accessed 15 August 2005]  
This is a continuously updated concise review on the treatment of CFS.
- 68** Edmonds M, McGuire H, Price J. Exercise therapy for chronic fatigue syndrome. *Cochrane Database Syst Rev* 2004; (3):CD003200.  
This is a systematic review on exercise therapy for CFS.
- 69** Kop WJ, Lyden A, Berlin AA, *et al.* Ambulatory monitoring of physical activity and symptoms in fibromyalgia and chronic fatigue syndrome. *Arthritis Rheum* 2005; 52:296–303.
- 70** Wallman KE, Morton AR, Goodman C, *et al.* Randomised controlled trial of graded exercise in chronic fatigue syndrome. *Med J Aust* 2004; 180:444–448.  
The most recent randomized controlled trial of graded exercise in CFS measured not only the physical outcomes but also psychological and cognitive outcomes.
- 71** Whitehead L, Campion P. Can general practitioners manage chronic fatigue syndrome? A controlled trial. *J Chronic Fatigue Syndr* 2002; 10:55–64.
- 72** Huibers MJ, Beurskens AJ, Van Schayck CP, *et al.* Efficacy of cognitive-behavioural therapy by general practitioners for unexplained fatigue among employees: Randomised controlled trial. *Br J Psychiatry* 2004; 184:240–246.  
This was a negative study of CBT delivered by general practitioners.
- 73** Ridsdale L, Godfrey E, Chalder T, *et al.* Chronic fatigue in general practice: is counselling as good as cognitive behaviour therapy? A UK randomised trial. *Br J Gen Pract* 2001; 51:19–24.
- 74** Ridsdale L, Darbishire L, Seed PT. Is graded exercise better than cognitive behaviour therapy for fatigue? A UK randomized trial in primary care. *Psychol Med* 2004; 34:37–49.