

# The Neuroendocrinology of Chronic Fatigue Syndrome

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Chronic fatigue syndrome (CFS) is a common and disabling problem; although most likely of biopsychosocial origin, the nature of the pathophysiological components remains unclear. There has been a wealth of interest in the endocrinology of this condition, which will be reviewed in this article. Most studied has been the hypothalamic-pituitary-adrenal (HPA) axis; although the quality of many studies is poor, the overall balance of evidence points to reduced cortisol output in at least some patients, with some evidence that this is linked to symptom production or persistence. There is evidence for heightened negative feedback and glucocorticoid receptor function and for impaired ACTH and cortisol responses to a variety of challenges. However, there is no evidence for a specific or uniform dysfunction of the HPA axis. Given the many factors that may impinge on the HPA axis in CFS, such as inactivity, sleep disturbance, psychiatric comorbidity, medication, and ongoing stress, it seems likely that HPA axis

disturbance is heterogeneous and of multifactorial etiology in CFS. Studies assessing GH, dehydroepiandrosterone and its sulfate, melatonin, leptin, and neuroendocrine-monoamine interactions are also reviewed. There is some evidence from these studies to suggest alterations of dehydroepiandrosterone sulfate function and abnormal serotonin function in CFS, but whether these changes are of functional importance remains unclear. To obtain a clearer assessment of the etiological and pathophysiological relevance of endocrine changes in CFS, it is suggested that more prospective cohort studies be undertaken in groups at high risk for CFS, that patients with CFS are followed up into recovery, and that multidimensional assessments are undertaken to unravel the influence of the various confounding factors on the observed endocrine changes in CFS. (*Endocrine Reviews* 24: 236–252, 2003)

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## I. Introduction

CHRONIC FATIGUE SYNDROME (CFS, but popularly known as chronic fatigue and immune dysfunction syndrome, or CFIDS, in the United States and myalgic encephalomyelitis, or ME, in the United Kingdom) is a disorder characterized by profound disabling chronic fatigue in association with a number of other symptoms. Although it most likely represents the end of a continuum, as is the case with severe hypertension, research has been facilitated by the introduction of consensus criteria for the condition. Operationally defined, the fatigue must be severe enough to cause a significant loss of physical and social function for a minimum of 6 months, and four of the following symptoms must also be present: sleep disturbance (usually unrefreshing sleep or hypersomnia), concentration impairment, muscle pain, multijoint pains, headaches, postexertional exacerbation of fatigue, sore throat, and tender lymph nodes (1). Exclusions include a clear underlying organic cause, substance misuse, and severe psychiatric disorder such as psychotic depression. Less severe psychiatric disorders such as major depression without *Diagnostic and Statistical Manual* (DSM)-IV-defined melancholic features or anxiety disorders are not exclusionary diagnoses and are frequently comorbid with CFS. It should be noted that this definition is currently under review, and a revised version derived from empirical validation is likely to be substituted [W. Reeves, Center for Disease Control (CDC), personal communication]. Chronic

Abbreviations: AVP, Arginine vasopressin; CBG, corticosteroid-binding globulin; CDC, Center for Disease Control; CFS, chronic fatigue syndrome; CSF, cerebrospinal fluid; DDAVP, desmopressin; DHEA, dehydroepiandrosterone; DHEA-S, DHEA sulfate; GR, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal; IST, insulin stress test; UFC, urinary free cortisol.

fatigue failing to meet these criteria is defined as idiopathic chronic fatigue, although there remains little evidence that this is a discrete category of patients. Other less-widely applied criteria also exist for CFS (2, 3).

Recent estimates of its prevalence in the community vary from 0.5–1.5% (4). However, the etiology of CFS remains elusive. Evidence exists for and against the importance of virological, immune, endocrine, psychological, and other factors as being etiologically important. Nevertheless, the most likely outcome is that it is a heterogeneous condition with a multifactorial etiology. It is also notable that the nature and causes of CFS have been the subject of much debate between sufferers and doctors, both at the level of the consultation and in the wider media (4).

The purpose of this article is to review the accumulated evidence linking CFS or similar states specifically to endocrine dysfunction. This will include not only studies looking directly at endocrine function, but also those using endocrine tests to assess other etiological factors, such as monoamine dysfunction.

## II. Methodological Considerations

There are numerous papers reporting results of some form of assessment of the various neuroendocrine axes. Many studies are unfortunately flawed to a greater or lesser degree. In this review, a critical approach will be taken to focus on the studies with the most merit. Among the considerations that will be applied are the following: 1) Methods of assessment: There are many methods of assessment of both basal and stimulated endocrine function, some of which have more validity than others. 2) Case definition: given the fact that fatigue is a common complaint, accurate application of consensus case definitions is vital. Similarly, conditions such as fibromyalgia have clear overlapping symptoms with CFS, and [notwithstanding misgivings about the nosological status of these conditions, *e.g.*, Wessely *et al.* (5) and Nimnuan *et al.* (6)] they may coexist. 3) Psychiatric comorbidity: Comorbid depressive illness is present in up to 50% of CFS patients (4). Because high circulating cortisol is a frequent occurrence in major depression (7), this may clearly affect the results of these studies. Similarly, atypical major depression, in which fatigue is a prominent complaint along with hypersomnia, hyperphagia, and rejection sensitivity, several studies have shown hypocortisolism and hypothalamic-pituitary-adrenal (HPA) axis disturbances (8). Other psychiatric disorders are also overrepresented in CFS, and there is evidence that, for example, somatoform disorders (9) or panic disorder (10) are also associated with HPA axis changes. It is therefore vital to assess accurately the psychiatric status of CFS patients who participate in endocrine studies. 4) Confounds: A great many factors can affect neuroendocrine function, and clear interpretation of any alterations in neuroendocrine function requires assessment and consideration of such factors. Important ones to measure include: past or current use of medication that might affect the HPA axis, sleep disturbance, habitual functional capacity/activity, energy expenditure during testing, and current psychosocial stressors.

## III. HPA Axis and CFS

### A. Historical aspects

Although often thought of as a new illness, in fact there are striking parallels between CFS and the Victorian concept of neurasthenia (4). Furthermore, although the suggestion that CFS might be related to HPA axis dysfunction first appeared in the scientific literature in the 1980s, earlier generations of physicians had already visited this ground. Thus, from 1902–1925 the term hypoadrenia or “a bit of Addison’s disease” was often used, although without firm scientific grounding (11). The more recent interest in the role of the HPA axis in CFS developed from the observations that conditions in which there is low circulating cortisol are characterized by debilitating fatigue. Thus, Addison’s disease (12), glucocorticoid withdrawal (13), and bilateral adrenalectomy (14) are all associated with fatigue and with other symptoms also seen in CFS, such as arthralgia, myalgia, sleep disturbance, and mood disorder (15). These observations led to the hypothesis that fatigue in CFS is mediated by low circulating levels of cortisol. The first study linking chronic fatigue to hypocortisolism was that by Poteliakhoff *et al.* in 1981 (16). This study found lower mean cortisol levels in 25 patients with fatigue for at least a month (but not necessarily meeting modern definitions of CFS) compared with 25 controls, based on a single morning plasma sample of cortisol. Many studies have now tested this hypothesis, allowing us to evaluate the level of empirical support for this contention.

### B. Studies of basal HPA axis function

Reviewing the literature, there is a wealth of studies that have reported an assessment of basal function of the HPA axis. At the most basic, these studies report single baseline measures of plasma cortisol, either as the primary focus of the study or as part of a subsequent dynamic test (16–32). Although a minority of these studies has reported lowered cortisol levels, usually in the morning, it is clear that such assessments are of very limited value: not only do they fail to allow for the stress of hospital attendance or cannulation/venepuncture, they are also inadequate in evaluating the function of a pulsatile hormone such as cortisol. This review will therefore focus on those studies that have undertaken serial measures of unstimulated cortisol and/or ACTH levels in blood or saliva and studies of 24-h urinary collections.

Six studies were identified in which either serial samples were taken to evaluate morning (33) or evening (17) cortisol levels, or samples were taken over an extended period of the day (34–37). Table 1 lists these studies. An additional six studies were identified that measured urinary free cortisol (UFC) in 24-h samples of urine (Refs. 17, 30, 35, and 38–40 and Table 2). Finally, five studies have used salivary cortisol measures (Refs. 40–43 and Table 3).

Summarizing these results, about half of the studies found some evidence for lowered cortisol levels at some point in the day. In terms of the methods of HPA axis assessment, the most striking results have been found with the studies of UFC. Indeed, the largest study of the HPA axis to date, which recruited 121 patients, found lowered levels of free cortisol (Ref. 39 and Fig. 1). On the plus side, these studies have

TABLE 1. Studies of basal HPA axis function: serial blood samples

Study	Subjects	Illness duration	Comorbid psychiatric illness (method of assessment stated, if any)	Method	Cortisol findings in CFS patients
Demitrack <i>et al.</i> (17)	19 CFS (CDC) 18 healthy	7.2 yr (mean)	Lifetime diagnoses: 7 major depression, 4 anxiety, 1 somatization disorder (DIS)	3 samples at 2000 h	Low
Moorkens <i>et al.</i> (34)	29 CFS (CDC) 9 healthy controls	1.5 yr	Major psychiatric disorders excluded (no structured interview)	5 samples between 2200 h and 0600 h	Low peak cortisol in CFS <i>vs.</i> controls
Hamilos <i>et al.</i> (35)	7 CFS (CDC) 7 controls 7 depressed 7 allergy	Not given	2/7 CFS had major depression, 1/7 CFS had panic disorder (DIS)	7 samples over 24 h	Low peak cortisol in CFS <i>vs.</i> controls
MacHale <i>et al.</i> (37)	30 CFS (CDC) 15 healthy	5.2 yr	Depression excluded (SADS)	2 samples at 0800 + 2200 h	No difference (but reduced diurnal variation in CFS)
Racciatti <i>et al.</i> (36)	24 CFS (CDC) 5 depressed 16 healthy	Not given	No data	6 samples over 24 h	No difference
Altemus <i>et al.</i> (33)	19 CFS (CDC) 19 healthy	3.7 yr	3 CFS had current anxiety disorder, 11 CFS had somatoform pain disorder; depression excluded, but mean HRSD = 13.8 (DIS)	5 samples at 0830–0930 h	No difference

HRSD, Hamilton Rating Scale for Depression; DIS, diagnostic interview schedule; SADS, schedule for affective disorders and schizophrenia.

TABLE 2. Studies of basal HPA axis function: urine

Study	Subjects	Illness duration	Comorbid psychiatric illness (method of assessment stated, if any)	Method	Cortisol findings in CFS patients
Demitrack <i>et al.</i> (17)	19 CFS (CDC) 18 healthy	7.2 yr (mean)	Lifetime diagnoses: 7 major depression, 4 anxiety, 1 somatization disorder (DIS)	UFC over 4 d	Low
Scott and Dinan (38)	21 CFS (CDC) 10 depressed 15 healthy	Not given	5 CFS had depression (unstructured psychiatric interview)	24-h UFC	Low No difference between depressed and nondepressed CFS
Cleare <i>et al.</i> (39)	121 CFS (CDC) 64 healthy	5.4 yr	32 current psychiatric comorbidity, 59 lifetime psychiatric comorbidity (assessment by psychiatrist using SSI-CFS)	24-h UFC	Low No difference between depressed and nondepressed CFS
Cleare <i>et al.</i> (30)	37 CFS (CDC + Oxford) 28 healthy	3.6 yr	No psychiatric comorbidity (assessment by 2 psychiatrists using SSI-CFS)	24-h UFC	Low
Hamilos <i>et al.</i> (35)	7 CFS (CDC) 7 controls 7 depressed 7 allergy	Not given	2/7 CFS had major depression, 1/7 CFS had panic disorder (DIS)	24-h UFC	No difference
Young <i>et al.</i> (40)	22 CFS (CDC) 22 healthy	2.5 yr	Depression and anxiety excluded (SCAN)	24-h UFC	No difference

DIS, Diagnostic interview schedule; SSI-CFS, semistructured interview for CFS (160); SCAN, structured clinical assessment for neuro-psychiatry.

(cumulatively) the largest number of participants. However, on the negative side, there are problems with using UFC measures. For example, it has been argued that 24-h UFC is an unreliable indicator of HPA activity (44). Assays for cor-

tisol have a large variability at the lower end of the spectrum, making its use for detecting low levels less precise. Furthermore, free cortisol only represents 2–3% of the circulating cortisol metabolites (45); thus, any shift in cortisol metabolic

TABLE 3. Studies of basal HPA axis function: saliva

Study	Subjects	Illness duration	Comorbid psychiatric illness (method of assessment stated, if any)	Method	Cortisol findings in CFS patients
Wood <i>et al.</i> (41)	10 CFS (CDC + Oxford) 10 healthy	3.75 yr	Depression excluded (assessment by psychiatrist using SSI-CFS, but 5/10 had high Beck Depression scores)	16 hourly samples from 0700–2200 h	High
Stickland <i>et al.</i> (42)	14 CFS (CDC + Oxford) 26 depressed 131 healthy	Not given Recruited from medical outpatient dept.	10 CFS had depression (LSA)	2 morning samples on consecutive days	Low
Young <i>et al.</i> (40)	22 CFS (CDC) 22 healthy	2.5 yr	Depression and anxiety excluded (SCAN)	4 samples from 0800–2000 h	No difference
Gaab <i>et al.</i> (43)	21 CFS (CDC + Oxford) 21 healthy	5.6 yr	7 past history of depression, 4 past history of anxiety, 1 current depression (DIA-X)	Waking curve (1, 15, 30, 45, and 60 min after awaking) Day curve (4 samples from 0800–2000 h)	No difference No difference
Cleare (123)	56 CFS (CDC) 38 healthy controls	5.2 yr	40% had depression (SCAN)	Waking curve (1, 10, 20, 30, and 60 min after awaking) Day curve (4 samples from 0800–2000 h)	Low No difference compared to controls, but levels increased after cognitive behaviour therapy No effect of comorbid depression

SSI-CFS, Semistructured interview for CFS (160); DIA-X, Dia-X interview schedule (161); SCAN, structured clinical assessment for neuropsychiatry; LSA, Lewis' standardized assessment (162).

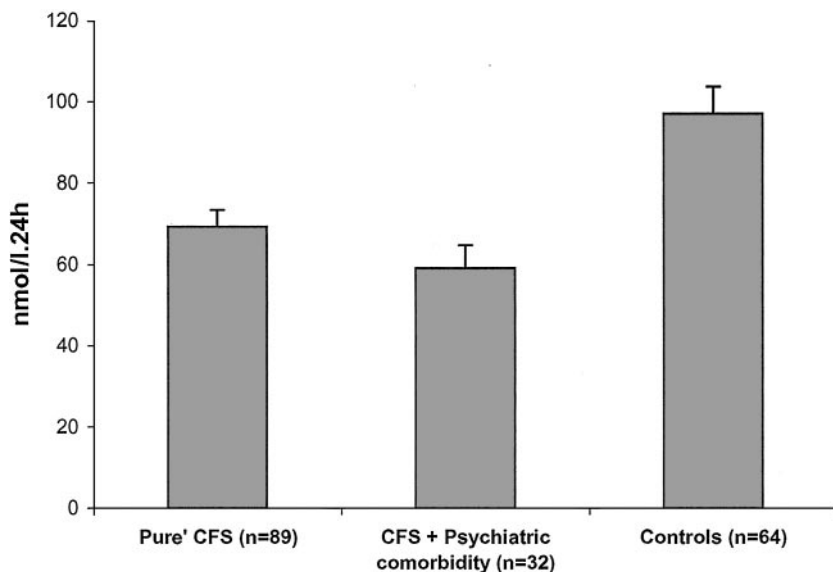


FIG. 1. Twenty-four-hour UFC output in patients with CFS without (Pure CFS) or with psychiatric comorbidity and in healthy controls. Graphical representation of data contained in paper by Cleare *et al.* (39).

pathways could potentially affect the measured UFC even if there were no change in cortisol production. Such a change has not been found in CFS to date when looked at (N. Taylor, personal communication) but can occur in major depression (46). It has also been proposed that commercially available kits for assessing UFC may systematically overestimate UFC in urine (47). One would like, therefore, to see corroboration from other methods. The results using salivary cortisol, which has several advantages [e.g., a noninvasive collection

method, ability to be undertaken in naturalistic settings, measuring biologically active free cortisol (48)] are clearly less supportive, and those using blood intermediate.

Preliminary reports from a recent meta-analysis of all studies of 24-h UFC and morning and afternoon plasma cortisol levels found a moderate overall effect size for reduced 24-h UFC (−0.73) and morning cortisol (−0.35) but with substantial heterogeneity between studies and larger effects sizes in samples recruited from tertiary compared with primary care

(49). There were no differences in afternoon plasma cortisol levels. However, without additional details upon publication of this meta-analysis, it is difficult to assess what criteria were used in choosing studies. At present, there is insufficient evidence to make differential assessments of specific alterations in cortisol levels at specific times of the day.

### C. Challenge tests

Dynamic challenges of the HPA axis have been undertaken, first to attempt to detect more subtle disturbances of the axis that may be relevant to the pathophysiology of the disorder, in a similar way to investigation of other stress-related disorders such as major depression, and also to determine where in the pathway any abnormalities may exist to explain the mild hypocortisolism seen in some patients.

**1. CRH test.** The CRH challenge test has been the most widely used challenge test in CFS; four groups have now undertaken this test in CFS. The first study was published in 1991 by Demitrack *et al.* (17). They tested 19 adult patients with CFS and 18 controls, although there were apparent differences in age and sex distribution between the groups. Furthermore, many subjects had comorbid psychiatric disorders, and the mean duration of illness was 7.2 yr. They used 1  $\mu\text{g}/\text{kg}$  ovine CRH administered at 2000 h and found blunted ACTH responses but normal cortisol responses. Their explanation for this result (taken in combination with the results from a series of administered challenge tests) was that there was a reduced suprahypothalamic stimulus to the HPA axis, with compensatory secondary up-regulation of the adrenal cortex responsiveness to ACTH.

A second group (23) also administered ovine CRH, though at a different dose (100  $\mu\text{g}$ ) and at a different time (1300 h). They also tested a sample of adult CFS patients that did not have any current comorbid psychiatric disorder. Most were medication free, although two were taking hormone replacement therapy and one a steroid inhaler for asthma. They also reported attenuated ACTH responses to exogenous ovine CRH, but this time accompanied by reduced cortisol responses. However, whereas Demitrack *et al.* (17) had found high basal levels of ACTH, outruling impaired function of the pituitary corticotrophs, Scott *et al.* (23) found normal basal levels of ACTH. Thus, they suggested that down-regulation of CRH receptors on the pituitary corticotrophs was a possible explanation.

The largest study to date, by Cleare *et al.* (30), found different results than these two studies. They compared 37 adult patients with CFS, both medication and comorbid psychiatric disorder free, and 28 healthy controls. They used 1  $\mu\text{g}/\text{kg}$  human CRH administered at 0900 h. ACTH responses were normal in this sample, whereas it was the cortisol responses that were blunted. The authors argued that the previous finding of impaired ACTH responses to CRH could be explained by other factors in the samples, including medication and psychiatric comorbidity, especially because such a picture is characteristic of major depression (50).

The final study investigated a distinct subgroup of subjects with CFS: adolescent girls (age 11–17 yr) rather than adults (28). They administered 100  $\mu\text{g}$  CRH between 1300

and 1400 h, although whether this was the human or ovine form is not specified. There were no differences apparent among their 15 subjects and 14 matched controls. The relationship between CFS (and other conditions) in childhood and adolescence and adulthood remains uncertain, and this study is not directly comparable to the other three for this reason.

Conclusions must remain tentative from these different studies. Once again, there are significant differences in the test protocols that make comparison difficult, such as the use of ovine or human CRH, the doses used, and the sample characteristics including psychiatric comorbidity, medication use, time of testing, and sex matching. Furthermore, the case definition used by the CDC changed between 1988 and 1994 (1, 51, 52) to become less dependent on the number of physical symptoms present; thus, the populations may have differed because of this, too.

**2. Arginine vasopressin (AVP).** AVP acts synergistically with CRH to promote ACTH release (53, 54). The ACTH response to AVP is critically dependent on central levels of CRH, because this response is potentiated by coadministration in a dose-dependent manner and covaries with the circadian changes in hypothalamic CRH (55, 56). Thus, Altemus *et al.* (33) argued that the ACTH response to AVP acts as an indirect index of ambient hypothalamic CRH levels, especially in the morning, when CRH levels are relatively high. They compared the effects of a 1-IU/kg·min infusion of AVP over 60 min in 19 medication-free CFS patients (although none had current depression, 3 of 19 had current anxiety disorders, 11 of 19 had other somatoform disorders, and 16 of 19 had a prior psychiatric history) and 19 controls. They found a reduced ACTH response in the CFS patients, which they attributed to a lower ambient level of hypothalamic CRH. However, as the authors admit, several other explanations for the findings are possible.

For example, there may in fact be abnormalities with AVP release or receptors. Scott *et al.* (23) hypothesized that a deficit in endogenous AVP could contribute to the attenuated ACTH response they found with exogenous CRH stimulation. Supporting this, Bakheit *et al.* (57) found basal levels of AVP to be significantly reduced in response to water-deprivation challenge in CFS patients. Further support for this came from Scott *et al.* (26), who used desmopressin (DDAVP), an AVP analog, both alone and in coadministration with CRH. They found that, as in their original study, there were blunted ACTH and cortisol responses to 100  $\mu\text{g}$  of ovine CRH in CFS patients. DDAVP alone had a negligible effect in both groups. However, the coadministration of a 10- $\mu\text{g}$  bolus of DDAVP was able to normalize this effect such that both CFS and healthy controls had the same ACTH and cortisol responses. They hypothesized that this was due to up-regulated AVP receptors on the pituitary in CFS, consistent with a hypothesized hypothalamic AVP deficiency.

**3. ACTH test.** Demitrack *et al.* (17) undertook a careful dose-response study of 12 CFS and 10 healthy controls in which 4 doses of ACTH (Cortrosyn at 0.003, 0.01, 0.1, and 1.0  $\mu\text{g}/\text{kg}$ ) or placebo were administered on 5 separate days at 1800 h. Once again, there was a high rate of comorbid depression.

Dose-response curves were significantly different in patients and controls: at low doses of ACTH, only CFS subjects showed cortisol rises above placebo, suggesting a hypersensitivity of the adrenal cortex to ACTH. However, at higher doses of ACTH, cortisol responses were significantly lower than controls, suggesting an overall reduced maximal secretory capacity of the adrenal cortex.

A second study (24) used only one dose of ACTH (Synacthen), the standard 1- $\mu$ g low-dose challenge (58, 59), administered at 1400 h. They demonstrated an inverse relationship between the baseline cortisol and the incremental cortisol rise in response to ACTH, again suggesting hypersensitivity of the adrenal cortex to ACTH in CFS subjects with impaired HPA activity. They also found significantly attenuated cortisol responses overall, which they interpret as reflecting a diminished adrenocortical reserve secondary to reduced stimulation from an impaired pituitary output of ACTH.

However, Hudson and Cleare (60) repeated the 1- $\mu$ g Synacthen challenge in 20 nondepressed, medication-free CFS subjects, this time administered at 1200 h. There was no difference in cortisol response in comparison to a matched control group, although in males there was a trend toward a blunted response.

4. *Insulin stress test (IST)*. Although a preliminary study of 9 patients had suggested some abnormal responses during the IST (19), a more thorough study administered this test to 16 medication-free CFS subjects with no comorbid depression and 16 matched healthy controls (30). There was no difference in ACTH or cortisol responses. This was confirmed in another center in a large sample (34). However, a recent study (32) found a blunted ACTH response but normal cortisol response to the IST. Because the IST remains the gold-standard test for adrenal insufficiency, this suggests that CFS is not associated with frank hypocortisolism. However, such an approach is probably too blunt to be useful in detecting more subtle changes.

5. *Feedback tests and glucocorticoid receptor (GR) function*. One of the theories regarding the underlying cause of hypocortisolism in CFS is that of enhanced negative feedback of corticosteroid receptors on the hypothalamus or pituitary. One of the first studies did not specifically investigate CFS itself, but was an ambitious epidemiological study, administering questionnaire measures and a standard 1-mg overnight dexamethasone suppression test to 266 community-dwelling subjects (61). From these, the authors identified 41 subjects who scored positive on simple measures of fatigue. They found no relation between postdexamethasone cortisol levels and fatigue, although there was a positive correlation between depression level and postdexamethasone cortisol levels.

However, preliminary reports of studies in patients with CFS using dexamethasone (62) or hydrocortisone infusion (63) did suggest that CFS may be associated with heightened negative feedback. The most convincing evidence to date of an enhanced feedback sensitivity of GRs comes from a carefully conducted recent study by Gaab *et al.* (Ref. 43; see Table 3 in this review for details). They used sal-

ivary cortisol measures before and after low-dose dexamethasone (0.5 mg), a regimen more sensitive to hyper-suppression than the standard 1-mg test used in depression. There was evidence of heightened negative feedback in CFS patients compared with controls, with reduced postdexamethasone salivary cortisol output seen in CFS. The authors note the similarity of this finding with other conditions related to stress, such as burnout syndrome (64), posttraumatic stress disorder (65), adolescents exposed to earthquake-related trauma (66), women with histories of childhood sexual abuse (67), and chronic pelvic pain (68), and hypothesize that precipitating or chronic stress in CFS patients may underlie the finding.

*In vitro* studies of feedback provide further support for enhanced GR sensitivity. Visser *et al.* (69) looked at CD4-positive T cells from a small group of subjects with CFS. They found that a lower concentration of dexamethasone was needed to inhibit CD4 function, suggesting increased sensitivity to dexamethasone. Visser *et al.* (70) followed up this study by measuring GR function directly on the peripheral blood mononuclear cells of 10 subjects with CFS and 14 controls. Although there was no difference in GR affinity or number, or of GR mRNA expression, the peripheral blood mononuclear cells from patients with CFS were again more sensitive to dexamethasone, suggesting an abnormality in signal transduction beyond the level of receptor binding. These findings by Visser *et al.* are in keeping with the *in vivo* studies of GR function by Gaab *et al.* described above.

There are two studies that do not support enhanced GR function in CFS. One small study (71) reported a reduced GH response to dexamethasone. However, this study is problematic because this is a nonstandard test, the sample was also suffering from irritable bowel syndrome and fibromyalgia, and GH function itself may be disturbed in CFS (see Section IV). Kavelaars *et al.* (28) found a reduced effect of dexamethasone on white cells, using T cell proliferation as the marker; however, this was in adolescents and cannot easily be extrapolated to adults, because the presentation of functional symptoms, the continuity with adulthood, and the function of the endocrine system may differ substantially during the period of adolescence.

Overall, then, the evidence for enhanced negative feedback and GR function is fairly consistent in the relatively small number of published studies to date.

#### D. *Dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S)*

DHEA and DHEA-S are derived from the zona reticularis of the adrenal, as opposed to glucocorticoids, which are produced in the zona fasciculata. DHEA-S circulates at levels of about 1 order of magnitude greater than those of cortisol. Reductions in circulating DHEA and DHEA-S have been associated with a number of age-related conditions including coronary artery disease, memory impairment, and type 2 diabetes (72). The exact role of DHEA/DHEA-S remains unclear, although there are some theoretical links between these hormones and mood and energy. For example, in a large cross-sectional study, DHEA and DHEA-S were found

to be inversely correlated with depression scores (73), and treatment of depressive disorder with DHEA has been successful (74). Also of interest is the recent finding that replacement doses of DHEA in Addison's disease provide benefits to psychological well-being over and above those seen with hydrocortisone replacement (75).

The results of studies (22, 27, 29, 31, 76, 77) investigating basal DHEA and DHEA-S function are summarized in Table 4. Once again, an inconsistency between studies is notable, although some impairment is apparent in the majority. However, all but one study assessing basal function used a single DHEA sample, and one an overnight urine collection. Two of the studies reporting low DHEA levels did not exclude patients on medication (22, 29). Furthermore, the presentation of clinical data about the participants is poor in several studies. How any DHEA/DHEA-S abnormalities relate to changes in cortisol function has not been adequately addressed; in particular, there has been no measure of the

cortisol/DHEA ratio, felt to be a more biologically relevant measure by some. The role of dynamic challenge tests in assessing DHEA function is also unclear, although Scott *et al.* (77) note that DHEA represents one of the stress hormones released by the adrenal cortex.

Although the finding of low DHEA/DHEA-S in some of these studies has led to tests of DHEA as a therapy (described in Section III.F), it seems premature to conclude that there are clear changes in DHEA or DHEA-S in CFS.

#### E. Opioidergic studies

The opioidergic system exerts a predominantly inhibitory influence upon the HPA axis in man (78). Scott *et al.* (25) hypothesized that down-regulation of the HPA axis in CFS might be secondary to increased opioidergic tone. To test this, they administered naloxone, an opiate receptor antagonist, to 13 CFS patients. Naloxone reduces the inhibitory

TABLE 4. Studies of DHEA/DHEAS

Study	Subjects	Illness duration	Comorbid psychiatric illness (method of assessment stated, if any)	Method	Cortisol findings in CFS patients
Kuratsane <i>et al.</i> (22)	17 CFS (CDC) 35 healthy	Not given	No data	1 blood sample at 0900 h	Basal DHEA: no difference Basal DHEAS: low
De Becker <i>et al.</i> (76)	49 CFS (CDC) 35 healthy	Not given	No data	Overnight urine collection	17-ketosteroids sulfate: low
	22 CFS (CDC) 14 healthy	Not given	Primary psychiatric disorders excluded	1 blood sample at 0900 h 250 µg ACTH (Synacthen) challenge test	Basal DHEA: no difference DHEA response: low in CFS
Scott <i>et al.</i> 1999 (27)	15 CFS (CDC) 15 major depression 11 healthy	Not given	Free from comorbid psychiatric illness (SCID)	1 blood sample at 1200–1400 h	Basal DHEA: low in CFS ( <i>cf.</i> both healthy and depressed controls) Basal DHEAS: low in CFS ( <i>cf.</i> healthy controls)
Scott <i>et al.</i> 2000 (77)	19 CFS (CDC) 10 healthy	Not given	Free from comorbid psychiatric illness (SCID)	1 blood sample at 1200 h 1-µg ACTH (Synacthen) challenge test	Basal DHEA: no difference DHEA response: no difference DHEA/cortisol ratio: no difference at baseline, but trend for differential change over time
Ottenweller <i>et al.</i> (31)	17 CFS 14 healthy	All <6 yr (mean not given)	No major psychiatric diagnosis in 5 yr prior to illness onset; 9/17 CFS had current major depression (Q-DIS).	1 blood sample—time not stated Exercise to exhaustion	Basal DHEAS: no difference DHEAS response: no difference
Van Rensburg <i>et al.</i> (29)	15 CFS (CDC) 15 healthy	Not given	No data	1 blood sample at 0830 h	Basal DHEAS: low [in CFS females (n = 10) v control females (n = 10)]
Cleare <i>et al.</i> (163)	16 CFS (CDC) 16 healthy	2.5 yr	Free from comorbid psychiatric illness (assessment by 2 psychiatrists using SSI-CFS)	1 blood sample at 0900 h 1-µg/kg CRH challenge test	Basal DHEA: high Basal DHEAS: no difference DHEA response: no difference

SCID, Structured clinical interview for DSM-III-R; Q-DIS, quick diagnostic interview schedule; SSI-CFS, semistructured interview for CFS (160).

tone, thus producing an acute rise in ACTH levels. CFS subjects showed an attenuated ACTH response to naloxone, contrary to their prediction that the hypothesized increased opioidergic tone would produce a heightened ACTH response. Although there are difficulties in interpreting the results of antagonist challenges such as the naloxone test, Scott *et al.* hypothesized that there might be reduced opioidergic tone in CFS, further supported by the decreased  $\beta$ -endorphin levels found in another study (79). Decreased opioidergic tone has previously been shown in pain-prone individuals (80) and could theoretically contribute to the symptoms of myalgia, arthralgia, and headaches, which are part of the CFS symptomatology (1).

#### F. Treatment studies

If low circulating cortisol may mediate some or all of the symptoms in CFS, replacement of the hypothesized deficiency should lead to improvements in those symptoms. There have been two randomized, controlled trials testing this hypothesis. The first, by McKenzie *et al.* (81), prescribed hydrocortisone in a pattern approximating the normal diurnal variation in cortisol [13 mg/m<sup>2</sup> (about 20–30 mg) at 0800 and 3 mg/m<sup>2</sup> (about 5 mg) at 1400, daily]. Seventy patients with CDC-defined CFS, many with comorbid psychiatric diagnoses, received either active or placebo treatment for 3 months. There was a moderate but significant benefit on a global health scale, although not on other more specific measures of fatigue or disability. However, there was significant adrenal suppression in 12 of 33 patients on hydrocortisone. A second study (82) used much lower doses of 5–10 mg, chosen to represent a dose likely to replace the observed reduction of approximately 30% in 24-h UFC seen in previous studies. Thirty-two subjects entered a cross-over study, with 28 d on each treatment. There was a clinically significant fall in fatigue scores in 34% on active treatment (28% returning to levels of fatigue at or below the population median score), compared with 13% (9%) on placebo. There were large reductions in self-rated disability scores in those whose fatigue improved. Furthermore, on this dose of hydrocortisone, there was no significant adrenal suppression, and there were no serious adverse effects.

What was the mechanism of this improvement? Although overall the pretreatment endocrine status could not predict who would respond to treatment, those patients who responded to treatment showed a normalization of their pretreatment blunted cortisol response to CRH (30). Similarly, there were other measurable physiological effects of hydrocortisone (such as increased leptin levels) that differentiated responders from nonresponders (83), suggesting that those who responded may have had up-regulated GRs. Overall, these findings support the contention that low cortisol levels may be one factor contributing to symptoms and disability in CFS. However, the second treatment study (82) was short term only, and the positive effects wore off rapidly on the switch to placebo; thus, routine use of this strategy as a treatment is not recommended without further evaluation.

A similar approach has been suggested for DHEA, although as previously discussed, the evidence that it is reduced in CFS is conflicting. A pilot study of the adminis-

tration of DHEA was undertaken in 23 female subjects with CFS who were specifically chosen to have suboptimal levels of DHEA at baseline (defined as <2.0  $\mu$ g/ml; Ref. 84). Subjects received a mean dose of 58 mg/d for 6 months in an open study, with mean DHEA-S levels rising from 0.88–4.12  $\mu$ g/ml. Modest improvements were seen in fatigue, pain, and mood, but the open nature of the study, the selected nature of the subjects, and the lack of a placebo control group limit any conclusions that can be drawn from this.

The use of fludrocortisone has been tried because of the presence of autonomic disturbances in CFS. Although uncontrolled studies were positive (85), subsequent randomized trials have shown this to be an ineffective strategy (86, 87).

All treatment studies in CFS have relied heavily on self-reported measures of fatigue and disability. On one hand, this could be problematic because self-reporting may be biased by many factors, and as such may not accurately represent illness severity. On the other hand, one of the hypotheses about the etiology of CFS involves a distortion of the sense of effort (88); reversal of such a distortion would be apparent on self-report measures. Nevertheless, further work in CFS treatment ought to include more objective measures alongside subjective ratings, such as actigraphic measures of activity levels and patterns [*e.g.*, constantly underactive or showing a variable pattern of inactivity (89)]. These measures do not correlate well with reported fatigue (90) and may thus represent independent aspects of the illness.

#### G. Other

1. *Adrenal gland imaging.* The results from the ACTH challenge studies led to a study assessing adrenal gland size using computerized tomography (91). They found a significant reduction (adrenal gland atrophy, with reductions in right and left limbs of more than 50%) in 8 CFS subjects compared with a bank of 55 controls. However, because subjects were chosen specifically to have a blunted cortisol response to ACTH, the authors admit that this may not generalize to all CFS subjects; indeed, it is possible that normals selected for low cortisol responses would also show smaller adrenal glands.

2. *Cerebrospinal fluid (CSF) studies.* Demitrack *et al.* (17) measured CSF levels of CRH and ACTH in 19 CFS patients (again with high psychiatric comorbidity) and 26 controls at 0900 h after strict bed rest. No differences were apparent.

3. *Other challenges to the HPA axis.* Ottenweller *et al.* (31) used a maximal exercise challenge to the HPA, clearly of relevance given the exercise intolerance reported by CFS subjects. Seventeen CFS subjects and 14 controls (see Table 1 for details) were compared, with measures before, 4 min after, and 1 d after a period of exercise to exhaustion. CFS subjects showed a lower ACTH response immediately after this stressor, although cortisol responses did not differ. Interestingly, the time to exhaustion on the test was related to basal cortisol levels: lower plasma cortisol was associated with a shorter duration of exercise. There were no differences the following day, suggesting that endocrine disturbance is not related to the prolonged fatigue after exercise complained of by CFS

subjects. Gaab *et al.* (32) used two naturalistic, nonpharmacological challenges (exercise to exhaustion on a cycle ergometer and social stress using the Trier Social Stress Test) in CFS subjects and controls (see Table 1 for details). They found lower ACTH but normal cortisol responses to both challenges, similar to the pattern of response to the IST in this group of subjects. However, the differences in ACTH response disappeared when the lower baseline levels of ACTH in CFS subjects were controlled for.

**4. Genetics.** An exciting recent paper suggests that, in a small number of subjects with CFS, there may be a genetic basis for the observed HPA axis abnormalities. Torpy *et al.* (92) describe a pedigree in which they identified a novel mutation in the gene controlling the production of corticosteroid-binding globulin (CBG). The mutation was associated with a complete loss of function of CBG. Among the 32 family members tested, 3 were homozygous for the mutation and had no detectable CBG, whereas 19 were heterozygotes and had levels reduced by approximately 50% from the normal reference range. Total cortisol levels were very low in the homozygotes and positively correlated with CBG levels in the heterozygotes, but free cortisol levels were similar in all members. Of interest is the finding that 86% of the heterozygotes and two of three homozygotes had troublesome chronic fatigue that met the CDC criteria for idiopathic chronic fatigue. Five cases met full criteria for CFS. Pain syndromes and fibromyalgia were also common. The authors suggest that abnormalities in CBG may be related to the pathophysiology of fatigue in some cases and that known mutations for CBG be sought in cases of CFS or idiopathic chronic fatigue. They further suggest that those with identifiable CBG abnormalities may be the most likely to respond to hydrocortisone therapy (see Section III.F). Given that there is accumulating evidence of a genetic predisposition for chronic fatigue in general (93), further searches for specific genes mediating this may prove fruitful. However, reductions in CBG have not been found in CFS in general; studies have found raised levels (17), perhaps as a feedback response to lowered cortisol levels (94, 95).

#### H. Assessment and contribution of confounding factors

Evaluating the factors outlined in Section II, it is clear that many of the studies have not adequately assessed these other confounds. No study has measured all potential factors at the same time, and only a handful has attempted to assess the impact of individual factors. This remains a serious deficiency in the literature, although one often found in neuroendocrine studies in other fields, too.

**1. Psychiatric comorbidity.** Tables 1–3 note the results of psychiatric assessment in these studies, when carried out, but it should be noted that many studies failed to use gold standard structured psychiatric assessments. Thus, although the subjects studied by Wood *et al.* (41) were said to have had a diagnosis of major depression excluded by clinicians, 5 of 10 subjects had Beck Depression Inventory scores within the mild-to-moderate depression range. This could have accounted for a failure to find reduced salivary cortisol levels. The same reservations apply to the study by Altemus *et al.*

(33), whose negative findings were in apparently nondepressed CFS subjects who in fact had Hamilton Depression Rating scale scores consistent with mild depression. Similarly, the finding by Demitrack *et al.* (17) of impaired ACTH responses to CRH testing is also found in depression, and many of their subjects had comorbid psychiatric disorder. Nevertheless, even the results from both basal and dynamic studies that do rigorously exclude depressed subjects find mixed results. Only three studies have specifically assessed whether psychiatric comorbidity made any effect on observed results, only two of which had sufficiently large numbers to draw conclusions [studies of UFC (39) and salivary cortisol (123)]. In both cases, the presence of comorbid psychiatric disorder did not alter the observed lowered cortisol levels.

**2. Length of illness.** Another confounding factor is length of illness; the study by Demitrack *et al.* (17) that found lowered UFC values in CFS used subjects with a particularly long illness duration (mean 7.2 yr), whereas other studies that failed to find reduced basal cortisol levels used subjects that had been ill for much less time (40, 41). Thus, it would clearly be of interest to know how any endocrine changes evolve as CFS develops, because most studies are indeed undertaken on patients that have been ill for many years. Studies of high-risk cohorts will be useful to this end, and several such studies are ongoing. Preliminary results from one study, which measured salivary cortisol profiles in subjects with Epstein-Barr virus infection (who have a rate of CFS of around 15% 6 months afterward; Ref. 96) suggest no link between the development of chronic fatigue and low cortisol within this time frame (97).

**3. Premorbid factors.** It is also important to assess whether there are factors that could lead to trait HPA axis changes that would be present before the illness onset. One example might be childhood abuse; this has strong effects on the HPA axis (98, 99) and has also been linked to the etiology of patients with unexplained physical symptoms such as fatigue. No endocrine studies have assessed this.

**4. Sleep.** Disturbance in sleep can affect the HPA axis (100, 101). Surprisingly, given that sleep is so frequently affected in CFS, and is indeed one of the diagnostic features, little work has been undertaken to see whether this contributes to the endocrine dysfunction. Only one study has reported an attempt to do this, finding no link between a simple measure of self-reported sleep disturbance and 24-h UFC (39). More detailed sleep assessments and/or polysomnography seem warranted in future studies.

**5. Functional capacity and deconditioning.** Physical deconditioning and the stress of exercise can also have marked effects on the HPA axis (102). Little account of this has been taken in the literature. In one study, HPA axis change was not related to self-reported functional capacity (39). However, this was a self-reported measure, and actual activity was not measured. A more rigorous study did find that lowered basal cortisol levels were correlated with a shorter time to exhaustion on an exercise test (31). This could be interpreted either way; *i.e.*, it could be that those who were habitually less active

had lower cortisol levels and lower fitness; alternatively, it could be that those with lower cortisol levels (through whatever mechanism) had less energy capacity.

6. *Medication.* It is clearly important to exclude the possibility that any HPA axis changes are epiphenomena of medication. Most studies have in fact excluded subjects who were taking medication liable to affect the HPA axis, usually specifying a minimum medication-free period of 2 wk. One study found that both subjects on and off medication had low urinary cortisol levels (39).

### I. Comparison with other disorders

It has already been highlighted that there are a number of conditions that overlap in symptomatology co-occurrence with CFS. How different then is the endocrine profile between CFS and two of these conditions, CFS and fibromyalgia?

1. *Fibromyalgia.* Fatigue is an almost universal complaint in patients with fibromyalgia, and muscle pain is one of the items in the CFS diagnostic criteria. There is a large comorbidity between the conditions (4), and indeed some authors argue that they are manifestations of essentially the same condition (5). Of particular interest in this debate are the findings from neuroendocrine studies, which show several similarities to those in CFS. These similarities include several studies that have demonstrated reduced 24-h UFC in patients with fibromyalgia (103–105). As in CFS, other studies find normal UFC levels (106) or raised salivary cortisol levels (107). Other similarities include the findings of blunted cortisol responses to a variety of challenges, including exhaustive physical exercise (108), exogenous CRH (104), exogenous ACTH (109), and the IST (109, 110). However, three studies have found exaggerated ACTH responses to CRH and/or IST stimulation (104, 111, 112). Although other studies have not found this (110, 113), none of the pharmacological challenge studies in CFS has revealed significantly raised ACTH responses; thus, this difference between CFS and fibromyalgia seems significant. Demitrack (114) suggests that these different ACTH responses may in fact represent differences in AVP tone: whereas in CFS, AVP levels were found to be low (57), in fibromyalgia they were found to be high compared with controls, in response to postural challenge (104). Because AVP acts in synergy with CRH to release ACTH, a difference in AVP levels would be consistent with the differences demonstrated in ACTH responses for the two syndromes.

Methodological problems, of course, also exist in the fibromyalgia literature; a detailed critique is out of the scope of this review, but it will suffice to say that many of the difficulties in the CFS literature are also apparent in the fibromyalgia literature. More careful delineation of the factors affecting the HPA axis in the two syndromes may reveal what is common and what is unique in the etiologies and manifestations of the two conditions.

2. *Depression.* It is well documented that there is HPA axis overactivity in a proportion of depressed patients, and that this proportion increases as the severity of the depression

increases and as the clinical features of the illness become more melancholic in nature (7). Findings from dynamic studies of major depression include a blunted ACTH response to CRH; this is the same finding as in CFS, but occurs in the setting of increased circulating cortisol levels, which would be expected to exert a feedback on the pituitary response. Other findings in major depression include increased CSF CRH levels, enlarged adrenal glands and an enhanced response to exogenous ACTH, and impaired negative feedback measured by the dexamethasone-suppression test (115). All of these differences are distinct from those seen in CFS. A theory of CRH overdrive has been postulated to underlie these changes (116).

However, the validity of a subtype of depression (atypical depression) has recently been established (117); two of the four defining symptoms of atypical depression are profound fatigue and unrefreshing hypersomnia, also two of the defining features of CFS. Furthermore, atypical depression has been shown to be characterized by underactivity of the HPA axis by demonstrations of hypersuppression to dexamethasone (118), lowered plasma cortisol levels (119, 120), and hypofunction of CRH neurons (8).

One hypothesis that may link the findings across these disorders is that there are common components to the illnesses that may be linked to the common HPA axis changes. Thus, the prominence of fatigue may be linked to the particular disturbance to the HPA axis in response to a stressor. Alternatively, common behavioral changes (altered sleep or reduced physical activity) that are common to the disorders may affect the HPA axis in similar ways. It might be possible to tease out a possible specific symptom link by focusing on subjects that have CFS but not muscle pain, fibromyalgia but not fatigue, atypical depression but not fatigue, *etc.* to determine this. Similarly, the presence of fatigue may be related to biological changes unrelated to the HPA axis, and insight into this could be obtained from other fatiguing illnesses.

### J. Summary and implications

There is no doubt that the quality of many studies of the HPA axis in CFS is poor. However, balancing the quality of studies, number of replications, consistency of findings, *etc.*, there appear to be indications that in some samples of CFS there is a mild, relative hypocortisolism; enhanced negative feedback with increased GR sensitivity; and impaired response of the HPA axis to activation. Although there is no evidence supporting any specific change to the HPA axis, almost all reports of changes to a wide variety of challenges are in the direction of blunting of ACTH or cortisol responses. There is also no convincing evidence that any HPA axis changes are specific to CFS or a primary cause of the disorder rather than being related to the many possible consequences or corollaries of the illness.

Reasons for the inconsistencies in findings are clearly apparent and include the heterogeneous nature of CFS itself, so that samples do differ even when the international case definition is used (121). The lack of assessment or control of the confounding factors may also contribute. However, there is also a suggestion that low-dose hydrocortisone therapy can improve fatigue in a minority of subjects, although it is not

known whether this is a specific finding. Nevertheless, it suggests that, even if low cortisol levels are a secondary or epiphenomenal finding, they may be contributing to fatigue perception or prolongation in some patients.

It is also not yet known what happens to CFS patients upon recovery from the illness. It might be hypothesized that clinical recovery would be paralleled by alterations in endocrine status. Studies using hydrocortisone replacement have been described already, but the most effective treatments so far discovered for CFS are nonpharmacological, namely graded exercise and cognitive-behavioral therapies (122). In a recently completed study (123), we found that cognitive-behavioral therapy led to improved symptoms and reduced disability in CFS, and HPA axis function was measured before and after therapy to see whether this improvement led to a reversal of the abnormalities present when those tests were performed in the same patients before treatment. Results from this type of study may prove informative.

#### K. Suggested theories for HPA axis dysfunction in CFS

Several attempts have been made to explain the underlying endocrine dysfunction in CFS. Those found in the literature include the following:

1) Demitrack *et al.* (17). These authors hypothesize that there is a deficient suprahypothalamic drive and reduced hypothalamic output of CRH. However, this would be expected to result in an up-regulation of pituitary CRH receptors, and consequently enhanced ACTH responses to exogenously administered CRH, the opposite to what has been found.

2) Scott and colleagues (23, 124). These authors have suggested that CFS is a stress-related disorder. They hypothesize that initial stress may cause an elevation in CRH with consequent down-regulation of CRH receptors on the pituitary corticotrophs. Secondly, they hypothesize that this down-regulation fails to normalize after the alleviation of stress, or the subsequent reduction in CRH levels, an example of abnormal plasticity in the CRH receptor. However, this is a similar hypothesis to that of major depression, and it is not clear how these authors link or separate these two conditions.

3) Cleare *et al.* (30). Primary pathology located in the adrenal glands has been suggested as an explanation for some findings, although why this might arise has not been elaborated.

4) Cleare and Wessely (125). These authors have hypothesized that there may in fact be a picture of chronic stress present in CFS, whether due to external or internal factors, that might explain the findings.

5) Heim *et al.* (9). These authors (and others) note the parallel between the endocrine finding in CFS and in a number of other disorders, including posttraumatic stress disorder, seasonal affective disorder, and atypical depression. They suggest that the findings may be a nonspecific marker of vulnerability to suffer from these conditions.

None of these theories provide a comprehensive understanding, and none are consistent with all findings from the research literature. Once again, it appears unlikely that there is a single explanation for the HPA axis changes seen in CFS.

#### L. Multidimensional assessment of HPA axis changes

In the final analysis, it seems unlikely that there is a specific or uniform change to the HPA axis in CFS. It seems more probable that the etiology of HPA axis changes in CFS is, like that of CFS itself, multifactorial. The presence of the many potential confounding factors makes it likely that a number of different alterations to the HPA axis may occur, depending on the presence of these various factors. An approach more likely to bear fruit in unraveling the etiology of HPA axis dysfunction in CFS would involve measuring more precisely the various confounding variables to allow a multidimensional understanding of HPA axis changes in CFS. Thus, future studies in CFS might include diurnal measures of sleep, physical activity, and neuroendocrine parameters; comprehensive dimensional psychiatric assessment; patients tested at different time points during the illness (*i.e.*, during acute, subacute, and chronic fatigue of varying durations); prospective cohort study designs; assessment of possible early life effects on the HPA axis, such as childhood abuse; and careful assessment of other factors, such as drugs (including the frequent use of herbal and other complementary medicines), diet, and psychosocial stresses, that might affect the HPA axis. It is perhaps the heterogeneity of these features in CFS in the different studies that underlie the divergent findings seen to date.

## IV. GH Axis

### A. Basal and dynamic challenge studies

The rationale for studying GH in CFS has come from several sources. First, there are parallel findings in the fibromyalgia literature, in which low GH function has been linked to sleep disturbances and muscle pain (126). It has recently become apparent that GH deficiency in adults is associated with some symptoms such as fatigue and myalgia (127). There are also suggestions that other fatigue states such as that occurring post operatively may be associated with GH changes (128).

In CFS, small preliminary studies suggested low basal GH, IGF-I, and IGF-II (129, 130), although this was not replicated in other studies (31, 131, 132). The study by Allain *et al.* (129) also demonstrated a reduced GH response to insulin-induced hypoglycemia, though Berwaerts *et al.* (130) failed to repeat this.

Two large and comprehensive studies have now been published investigating all aspects of the GH-IGF system. The first studied 37 CFS subjects and closely matched healthy controls (133). The authors failed to find any significant differences in either baseline or dynamic tests of GH function and concluded that there is no evidence for GH deficiency in CFS patients free from comorbid psychiatric illness. The second study also used basal measures of GH and the IST in 73 CFS patients and 23 healthy controls (see Table 1 for details) and additionally measured GH responses to clonidine (33 CFS patients and 6 controls) and arginine hydrochloride (39 CFS patients and 19 controls) in some subjects (34). In contrast to the first study, there was reduced nocturnal GH release and a reduced GH response to the IST in CFS. How-

ever, as in the first study there were no changes in IGFs, and the GH response to the other challenges was not blunted. Although some results seem conflicting between these two large studies, the latter study seemed to have less close age and sex matching of patients and control groups. It is not clear whether either study specifically excluded fibromyalgia subjects, in whom there is also evidence of GH abnormalities and who frequently also fill criteria for CFS. Similarly, the lack of a rigorous exclusion of depression may skew findings, given the finding in some studies of impaired GH function in depression (134).

### B. Treatment studies

Moorkens *et al.* (135) carried out a small, randomized, controlled trial of GH hormone replacement in CFS. They selected 20 patients with a demonstrated deficiency of GH, defined as a peak nocturnal level less than 10  $\mu\text{g}/\text{liter}$ . Patients entered a double-blind phase of 3 months on GH or placebo followed by a 9-month open phase. After 12 months of therapy, there was no overall improvement in questionnaire measures of quality of life, despite improvements in measures of GH function.

Overall, despite some abnormal findings, there seems little compelling evidence that GH dysfunction plays a major role in the symptomatology of CFS.

## V. Other Endocrine Factors

### A. Leptin

Comparison of basal leptin levels in 32 CFS subjects, medication free and with no psychiatric comorbidity, and matched controls found no differences (83). There is no evidence that disturbances in leptin metabolism may underlie appetite or weight symptoms in CFS.

### B. Melatonin

It has been suggested that melatonin supplementation might be beneficial for reported sleep disturbance in CFS (136). However, in a careful study, Knook *et al.* (137) measured nocturnal (1700–2000 h) saliva melatonin in 13 medication-free adolescents with CDC-defined CFS and 15 matched controls. They found increased levels in the patients, rather than the decreased levels they had expected to be associated with impaired sleep quality. In combination with findings of no difference (136) or increased (A. J. Cleare, M. Hudson, and A. Di Giorgio, unpublished data) melatonin levels in adult CFS, there appears to be no rationale for melatonin treatment in CFS. One interpretation of the increased levels of melatonin is that it represents a marker of increased susceptibility to stress-induced hypothalamic disruption (136).

## VI. Circadian Rhythms

Relatively few studies have attempted to measure circadian rhythms of hormones or other parameters in CFS. MacHale *et al.* (37) demonstrated a significantly attenuated

diurnal variation of serum cortisol in CFS, although the absolute concentrations at each time point were not significantly different compared with controls. Additionally, there was a significant relationship between the degree of diurnal variation in cortisol and measures of functional capacity. A similar finding of reduced diurnal variation seemed apparent in the study by Hamilos *et al.* (35), primarily related to a significantly reduced peak cortisol value. Further support for this comes from the demonstration of a significant decrease in the early morning surge of cortisol in a small group of CFS patients (138, 139). However, several other studies (36, 40, 41) have not found significant changes in diurnal variation in the circadian rhythm of cortisol (see Table 1 for details). Once again, any abnormalities found need to be evaluated in the context of similar changes being detectable in fibromyalgia, pain syndromes, and depressive illness (103, 140, 141).

Although most studies show the timing of the circadian cycle of pituitary hormone release or temperature to be essentially normal in CFS (35, 36, 142), one study did suggest a desynchronization of the temperature and melatonin rhythms (143).

## VII. Interactions with Monoamines

### A. 5-HT

There is a complex interaction between the HPA axis and serotonin systems in the brain. Many studies have demonstrated that glucocorticoids can have an inhibitory effect on central serotonin (5-HT) neurotransmitter function (144, 145), whereas, on the other hand, stress-induced CRH secretion is modulated by 5-HT (7, 146). Many studies have attempted to define the status of serotonergic systems in CFS by utilizing the neuroendocrine responses to challenge with serotonergic drugs. These drugs are thought to act on 5-HT pathways that project from the dorsal raphe nuclei to the paraventricular nucleus of the hypothalamus, which in turn effect secretion of hypothalamic peptides involved in the release of PRL and ACTH from the anterior pituitary (147). Therefore, measuring serial PRL and ACTH or cortisol responses to 5-HT agonist drugs give a putative index of hypothalamic-5-HT neurotransmitter function.

Several different serotonergic drugs have been used in CFS. The first study was by Bakheit *et al.* (148), who measured the PRL response to buspirone, a 5-HT<sub>1A</sub> receptor partial agonist. They found a significantly raised PRL response in CFS subjects compared with controls, suggesting up-regulation of postsynaptic 5-HT<sub>1A</sub> receptors in the hypothalamus. However, the specificity of buspirone has been questioned, because it also acts at dopamine D2 receptors, which may in part mediate PRL release (149, 150). Sharpe *et al.* (151) tested this by measuring the GH response in addition to PRL, because GH release is more likely to be mediated solely by 5-HT<sub>1A</sub> receptor stimulation (152). Although they confirmed an enhanced PRL response, GH responses were normal, consistent with the interpretation that abnormalities in dopamine rather than serotonin neurotransmission may underlie the enhanced PRL response.

Two studies have used the selective 5-HT-releasing agent *D*-fenfluramine, using either PRL or cortisol responses to

stimulation, and found evidence of enhanced serotonergic responses in nondepressed CFS subjects (18, 153). This is in contrast to the finding of impaired responses in major depression (18). Furthermore, serotonergic responses were inversely related to the basal cortisol levels. Thus, CFS patients had low baseline cortisol and enhanced serotonergic responses, and depressed subjects the converse. The authors suggested that HPA and 5-HT function may be pathologically altered in opposite directions in the two conditions, and also related to characteristic symptom profiles, such as insomnia, anorexia, and agitation in depression and the reverse of these in CFS. Two other studies found less clear-cut results (19, 20), perhaps due to methodological issues. Thus, in one study there was poor age and gender matching (19), and in another there was significant psychiatric comorbidity (20). In addition, the latter study used racemic D,L-fenfluramine, a preparation with both stereoisomers that is less neurochemically specific, also having additional catecholaminergic effects.

A final study has produced evidence suggesting a disturbance of the relationship between 5-HT and the HPA axis (21). Ipsapirone, a more specific 5-HT<sub>1A</sub> partial agonist than buspirone, was used to test the hypothesis that abnormalities of HPA function in CFS arise from disturbance in serotonergic (5-HT) inputs. In healthy controls, there was a dose-dependent rise in ACTH and cortisol, but in CFS the ACTH (but not cortisol) response was significantly attenuated. There are several possible explanations for the finding, including decreased responsiveness of 5-HT<sub>1A</sub> receptors responsible for controlling the HPA axis at the hypothalamic level. However, given the finding by this group of decreased responsiveness of pituitary CRH receptors (23), then reduced pituitary responsiveness is another possibility. Some support for there being an abnormality in 5-HT<sub>1A</sub> receptors comes from a recent positron emission tomography study showing reduced binding of the specific 5-HT<sub>1A</sub> radioligand WAY100635 (A. J. Cleare, C. Messa, E. Rabiner, and P. Grasby, unpublished data).

### B. Other neurotransmitters

1. *Noradrenaline.* The study of CSF and plasma by Demitrack *et al.* (154) revealed a reduction in the main metabolite of noradrenaline, MHPG. Of interest, therefore, is a study that suggested that fatigued athletes differed from nonfatigued athletes by having lower plasma noradrenaline (155). However, no other studies of noradrenergic function in CFS have been published.

2. *Acetyl choline.* There has been one study investigating the GH response to pyridostigmine, an anticholinesterase inhibitor. CFS patients showed enhanced responsiveness, suggesting up-regulated cholinergic receptors (156).

## VIII. Conclusions

CFS is most likely a heterogeneous condition with a multifactorial origin. One of these factors is likely to include disturbances to some neuroendocrine systems. Most studied to date has been the HPA axis, and overall the balance of

evidence is suggestive of abnormalities of HPA axis function in at least some patients. There is some evidence from the trials of replacement therapy that this is linked to symptom production or persistence. It remains possible that effects of central correlates of low circulating cortisol, such as CRH or serotonin abnormalities, mediate the effects on fatigue and other symptoms. Furthermore, given the many factors that may impinge on the HPA axis in CFS, such as inactivity, sleep disturbance, psychiatric comorbidity, medication, and ongoing stress, it seems likely that HPA axis disturbance is heterogeneous and of multifactorial etiology in CFS.

Recent conceptions of CFS have also separated out those factors that act as risk factors, or predisposing factors; those that act as triggers, or precipitating factors; and those that act to prolong the condition, or perpetuating factors (4). This approach has not yet been adequately applied to endocrine disturbances, because most studies have been undertaken on patients who had been ill for several years.

Thus, to obtain a clearer assessment of the etiological and pathophysiological relevance of endocrine changes in CFS, several future directions are likely to be useful. First, to study the importance of endocrine disturbances at the onset of the illness, as risk factors or triggers, it will be necessary to perform prospective cohort studies in groups at high risk of CFS, such as those after Epstein-Barr virus infection (157), major surgery (158), cancer (159), and similar groups. It will also be useful to test patients after recovery from CFS, to identify those abnormalities that may relate to symptoms, that may be epiphenomena, or that may be trait markers. Finally, the importance of undertaking full multidimensional assessments cannot be overstated; without details of the various confounding features outlined in this review, it is unlikely we will be able adequately to unravel the influence of the various confounding factors on the observed endocrine changes in CFS.

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