

# Neuroendocrine Aspects of Chronic Fatigue Syndrome

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## Key Words

Chronic fatigue syndrome · Neuroendocrine system · Hypothalamic-pituitary-adrenal axis · Cortisol · Autonomic nervous system · Immune system

## Abstract

Chronic fatigue syndrome (CFS) is a serious health concern affecting over 800,000 Americans of all ages, races, socioeconomic groups and genders. The etiology and pathophysiology of CFS are unknown, yet studies have suggested an involvement of the neuroendocrine system. A symposium was organized in March 2001 to explore the possibility of an association between neuroendocrine dysfunction and CFS, with special emphasis on the interactions between neuroendocrine dysfunction and other abnormalities noted in the immune and autonomic nervous systems of individuals with CFS. This paper represents the consensus of the panel of experts who participated in this meeting.

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## Introduction

Chronic fatigue syndrome (CFS), also known as chronic fatigue and immune dysfunction syndrome (CFIDS) and myalgic encephalomyelitis, is a serious health concern. A study by DePaul University estimates CFS prevalence at approximately 422/100,000 adults in the US [1]. This means as many as 800,000 people nationwide have the condition. Studies show that 85–90% of people with CFS have not been diagnosed and are not receiving appropriate medical care for their illness. It is nearly twice as common in women as men. To put CFS prevalence into perspective, systemic lupus erythematosus affects 50/100,000, multiple sclerosis affects 104/100,000, and rheumatoid arthritis affects 1,022/100,000 American adults.

CFS affects people of all races, ages, and socioeconomic groups. Additional data from the DePaul study found a significantly increased prevalence in minorities and persons in lower-income brackets, two populations that have not been previously recognized as being at greater risk

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than wealthier nonminorities for CFS, and which are generally underserved by the medical community. Of the people with CFS identified in this study, only 10% had been previously diagnosed, lending extra impetus to efforts to increase knowledge and awareness of CFS.

There are as yet no sensitive and specific diagnostic markers for CFS. To exclude other mental and physical causes of their symptoms, persons with CFS often must undergo an extensive battery of tests before the CFS diagnosis is considered.

To be diagnosed with CFS, a person must meet the following International CFS case definition criteria [2]: (1) unexplained persistent or relapsing fatigue for at least 6 months' duration that is of new or definite onset, not the result of ongoing exertion, is not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social, or personal activities and (2) four or more of the following eight symptoms, persistent or relapsing, for at least 6 months: impairment of short-term memory or concentration; sore throat; tender cervical or axillary lymph nodes; muscle pain; multijoint pain without joint swelling or redness; headaches of a new type, pattern or severity; unrefreshing sleep, and postexertional malaise lasting more than 24 h.

CFS seems to be a multisystem disorder. The etiology and pathophysiology of the syndrome are unknown. There have been a number of studies suggesting an involvement of the neuroendocrine and immune systems in the pathophysiology of CFS. For example, persons with CFS have been shown to have lower 24-hour urinary free cortisol excretion and low morning plasma cortisol concentration compared to normal controls. However, dynamic endocrine testing of the hypothalamic-pituitary-adrenal (HPA) axis has not been found to yield consistently abnormal results. Specifically, some studies have shown that persons with CFS demonstrate normal plasma cortisol responses to corticotropin-releasing hormone (CRH) stimulation, whereas other investigators have shown that cortisol responses to adrenocorticotropin hormone (ACTH) stimulation have been subnormal in this patient population. Thus, the nature of the abnormality of the HPA axis is unclear. Similarly, early findings of abnormalities in growth hormone (GH) secretion in CFS have not been confirmed by recent studies. In addition, the thyroid and reproductive hormone axes have not been adequately investigated. Inflammatory cytokines have been implicated in the pathogenesis of CFS as well; however, the data on this issue are controversial. Administration of inflammatory cytokines, such as interferon- $\gamma$  and interleukin-6 (IL-6), to human subjects results in fatigue

However, no conclusive and unequivocal cytokine abnormality has been identified in persons with CFS. Persons with CFS have abnormal and nonrestorative sleep, but the details of their sleep disorder remain to be elucidated.

This symposium, cosponsored by the CFIDS Association of America and the US Centers for Disease Control and Prevention, was designed to explore these issues and the possibility of an association between the neuroendocrine system and CFS and, if so, what that association might be.

This consensus statement was written by an independent panel of experts, composed of well-respected researchers and practitioners in the fields of endocrinology, neurology, psychiatry, sleep disorders, epidemiology, biostatistics, immunology, and internal medicine, as well as two patient representatives. This statement was based on (1) presentations by investigators working in areas relevant to the consensus questions during a 1-day scientific court session, (2) questions and statements from conference attendees during open discussion periods that are part of the scientific court session, and (3) closed deliberations by the panel during 1½ days.

The consensus panel weighed the scientific evidence and developed this statement in response to the following questions, posed by a scientific planning committee:

Question 1: (a) What is the evidence that there is an alteration in the HPA function in CFS? (b) What abnormalities in the HPA axis lead to symptoms common in persons with CFS? (c) Are there differences between people with CFS who do or do not have HPA axis abnormalities?

Question 2: What is the evidence of an interaction between cytokine abnormalities and neuroendocrine abnormalities, orthostatic intolerance (OI), and the symptoms common in persons with CFS?

Question 3: What is the evidence of the role of different types of stressors (i.e., viral or bacterial illness, physical or psychological trauma, chronic pain, etc.) on neuroendocrine function in disorders that are characterized by symptoms common in persons with CFS?

Question 4: What is the evidence of an interaction between sleep abnormalities and disruption of circadian rhythms of (a) cytokines, (b) hormones of the HPA axis, (c) GH, and (d) melatonin in CFS and in disorders characterized by symptoms common in CFS?

Question 5: Is there a link between the neuroendocrine profile in depression (melancholic and/or atypical) and CFS?

Question 6: (a) What are the recommendations for future research? (b) What are the recommended opportunities for research collaboration? (c) What methodological barriers are there to the careful study of these hypotheses?

This statement is an independent report of the panel and is not a policy statement of the CFIDS Association of America or the Centers for Disease Control and Prevention.

### **The CFIDS Association of America**

Founded in 1987, the CFIDS Association of America is the largest and most active charitable organization dedicated to conquering CFS. The association has invested more than USD 13 million in education, public policy, and research programs in its efforts to bring an early end to the suffering caused by CFIDS, including more than USD 3.4 million in grants to individual CFIDS researchers.

One of the association's goals is to facilitate research that seeks to uncover the mechanisms and potential causes of CFS. To contribute to the accomplishment of that goal, the association organized a symposia series to explore and assess the role of the cardiovascular, neuroendocrine, immune, and nervous systems in the onset, control, and progression of CFS. The primary purposes of these symposia are: to provide scientific evaluation of current research findings, to identify possible linkages, mechanisms, causalities, and the most promising next steps for research through the synergy of exchange, to define research and funding priorities, and to foster creation of research collaboration teams.

### **US Centers for Disease Control and Prevention**

The US Centers for Disease Control and Prevention (CDC) protects the nation's health and safety by preventing and controlling diseases and injuries, enhances health decisions by providing credible information on critical health issues, and promotes healthy living through strong partnerships with local, national, and international organizations. The agency conducts a CFS research program under the auspices of the National Center for Infectious Diseases.

### **Question 1**

*(a) What Is the Evidence that There Is an Alteration in the HPA Function in CFS?*

Activation of the HPA axis and the sympathetic nervous system comprises the two major components of the stress response in human beings. CRH and, to a lesser degree, vasopressin are released from the paraventricular nucleus of the hypothalamus and stimulate the anterior pituitary to release ACTH. ACTH in turn stimulates cortisol release from the adrenal cortex. HPA axis abnormalities have been studied using both basal and challenge paradigms in persons with CFS and fibromyalgia<sup>1</sup>, since early investigations suggested that these disorders represented a response to stressful stimuli.

The majority of studies have shown decreased basal cortisol production in persons with CFS. However, this finding is not universal. Some studies have failed to find abnormalities in basal cortisol production in these patients and at least in one study persons with CFS were found to have higher cortisol levels compared to normal controls. When dynamic testing of the HPA axis has been performed some studies have shown attenuated cortisol responses using a physiological challenge, such as a low-dose ACTH stimulation test, whereas other studies employing stronger stimuli, such as the insulin tolerance test, showed a normal cortisol response.

Variables that may explain the inconsistent results in these studies include the following: the remitting and relapsing nature of the illness, use of multiple research CFS case definitions, variability in interpretation of ambiguous case definition criteria terms, duration of illness, acute versus chronic stressors, severity of illness, body weight, gender, phase of the menstrual cycle, comorbid disorders, sleep disturbances, small sample sizes, and different study designs.

*(b) What Abnormalities in the HPA Axis Lead to Symptoms Common in Persons with CFS?*

Symptoms characteristic of CFS, such as fatigue, depressed mood, sleep disturbances, nausea, OI, myalgia,

<sup>1</sup> The American College of Rheumatology diagnostic criteria [3] for fibromyalgia include: widespread pain and the presence of 11/18 discrete tender points. Many persons with fibromyalgia also experience fatigue, stiffness, paresthesias, unrefreshing sleep, headaches, and gastrointestinal and bladder disturbances, which are symptoms common in CFS. Many clinicians consider these two syndromes to be overlapping, but not necessarily identical, conditions.

arthralgia, cognitive disturbances, and muscle weakness, are shared with conditions marked by either hypocortisolism or hypercortisolism. Addison's disease, or hypocortisolism, leads to symptoms of nausea, anorexia, OI, and muscle and joint pain. Hyperactivity of the HPA axis, as seen in Cushing's disease, is associated with cognitive disturbances and muscle weakness. Fatigue, depressed mood, and sleep disturbances can be found in either of these conditions.

HPA axis activity is tightly linked to the rest of the hypothalamic-pituitary unit. Hypercortisolism can lead to a decrease in GH secretion, which would in turn lead to symptoms seen in persons with CFS; specifically, GH deficiency has been associated with reductions in physical and mental energy and memory impairment in adult life. Severe hypoactivity of the HPA axis – such as the one seen in Addison's disease – can lead to a decrease in GH secretion as well.

Recently, mutations in the cortisol-binding globulin (CBG) gene have been identified in families with a high prevalence of a CFS-like illness. It is possible that the severely impaired cortisol binding capacity in these patients leads to inadequate delivery of cortisol to the target organs, leading to a state of functional hypocortisolism, despite the normal 24-hour urinary free cortisol excretion. Future studies should be undertaken to determine the role of CBG abnormalities in CFS.

*(c) Are There Differences between People with CFS Who Do or Do Not Have HPA Axis Abnormalities?*

There is no known study comparing persons with CFS with and without HPA axis abnormalities. However, studies with large enough groups and adequate controls should be performed and would provide much needed mechanistic approaches to the problem. In addition, longitudinal evaluation of the same study individuals over time would add to the validity and reliability of these findings. Persistence of findings over time would establish them as primary abnormalities rather than secondary to circumstantial confounding factors.

**Question 2: What Is the Evidence of an Interaction between Cytokine Abnormalities and Neuroendocrine Abnormalities, OI, and the Symptoms Common in Persons with CFS?**

Inflammatory cytokines, such as IL-6 and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), secreted during infection/inflammation, are potent stimulants of the HPA axis. In fact,

these cytokines participate in a negative feedback loop with the HPA axis. Cortisol, the final product of HPA axis stimulation, inhibits the secretion of IL-6 and TNF- $\alpha$ . Similarly, glucocorticoid deficiency leads to elevation of plasma concentration of the above cytokines. Secretion of these cytokines has been associated with symptoms expressed by persons with CFS. The most extensively studied among them are TNF- $\alpha$  and IL-6. IL-6, in particular, has been associated with somnolence, fatigue, anorexia, fever, and headache, and is a major factor in the pathogenesis of glucocorticoid withdrawal syndrome.

Inflammatory cytokines, IL-6 in particular, are closely associated with the autonomic nervous system. Administration of IL-6 in experimental models involving normal healthy individuals resulted in elevated plasma levels of norepinephrine, ACTH, and cortisol. In the same studies, persons with fibromyalgia exhibited exaggerated plasma norepinephrine levels and delayed, excessive plasma ACTH responses. However, the cortisol response was not different from that of normal healthy controls. In combination, these findings suggest a possible dysregulation of the stress system in patients with fibromyalgia.

These findings are interesting in view of the studies connecting CFS and OI. Reduced cortisol levels are associated with OI and hypotension in some individuals. There is evidence that excessive secretion of inflammatory cytokines, such as TNF- $\alpha$ , induces OI via increases in capillary permeability and the production of nitric oxide, which dilates vessels and produces hypotension. Studies further delineating the interrelationship between these two disorders are needed.

**Question 3: What Is the Evidence of the Role of Different Types of Stressors (i.e., Viral or Bacterial Illness, Physical or Psychological Trauma, Chronic Pain, etc.) on Neuroendocrine Function in Disorders That Are Characterized by Symptoms Common in Persons with CFS?**

A wide variety of stressors have been considered as possible triggers of CFS and related conditions. One of the originally hypothesized stressors causing CFS was a viral infection. Early studies suggested that chronic active Epstein-Barr virus (EBV) infections caused CFS. However, subsequent well-controlled studies examining a variety of EBV proteins could not substantiate a causal relationship. Additional viral and other infectious disease etiologies

have been suggested, such as parvovirus, enteroviruses, cytomegalovirus, retroviruses, herpes viruses, mycoplasmas, and even Borrelia burgdorferi. In an ongoing prospective study of the potential etiologic relationship between CFS and Q fever, Ross River virus, and EBV, preliminary results have shown that anergy during acute infection may predict persistent CFS symptoms. Carefully controlled studies of viral and other etiologies will be required to establish a causal relationship between the stress of infection and the development of neuroendocrinological disturbances in CFS.

In addition to the viral hypothesis of CFS, several studies have suggested that other noxious life events may also be stressors causing neuroendocrinological disturbances in CFS and related disorders. For example, physical trauma and motor vehicle accidents have been temporally associated with the onset of symptoms like those seen in CFS and fibromyalgia. In addition, catastrophic life events, such as combat experience and life-threatening illness, have been found to be followed by symptoms seen in CFS. Further elucidation of such potential causative factors is important.

Despite the suggestion that stressors and neuroendocrine dysfunction may play a role in conditions such as CFS, no studies have examined whether a relationship exists between these variables in persons with CFS. One small retrospective study has reported an increased prevalence of emotional, physical, and sexual abuse in adults with CFS and fibromyalgia, as compared to individuals with rheumatoid arthritis or multiple sclerosis or healthy controls. Studies connecting such stressors and neuroendocrine dysfunction have been limited to conditions such as posttraumatic stress disorder. For example, another small retrospective study of prepubescent females with a history of sexual abuse found decreased morning salivary cortisol compared to healthy controls. Prospective studies of the relationship between psychological trauma and the onset of CFS should be undertaken before conclusions are drawn about the role of life stress in CFS.

Several reports have suggested that the administration of commonly used medications like lipid-lowering drugs for the treatment of hypercholesterolemia and interferon- $\alpha$  administration for hepatitis C and other disorders may result in clinical symptoms similar to those reported by people with CFS. Examining the potential neuroendocrine mechanisms for these effects may shed light on neuroendocrine dysfunction in CFS.

Although neuroendocrine studies in some highly stressed individuals have shown hormonal response patterns similar to the ones seen in persons with CFS, there is

not enough evidence to establish the link between specific stressors and neuroendocrine findings in persons with CFS and related disorders.

One explanation for the relative lack of a direct relationship between a stressful life event and the immunoen-docrine disturbances seen in CFS is that recall of these events is based on the patient's self-report of remote experiences. Moreover, there is also a diversity of clinical presentations, in which some persons with CFS cannot recall stressful life events preceding their illness, while other individuals may experience life-threatening stressors without developing the syndrome.

While such studies must often rely upon patient self-reports, valid observations and testable hypotheses may still be derived from this process. The number of possible stressors in life is vast, and the number of stress-related triggers for CFS is large and broadly defined. Because of this, the study of carefully selected comparison subjects without traumatic events would be essential in research studies examining the causal relationship between stress triggers and neuroendocrine findings in CFS.

Finally, in order to examine the association between certain stressors and neuroendocrine disturbances in CFS, substantial patient numbers will be needed in future studies to validate findings from prior studies, which used small sample sizes.

**Question 4: What Is the Evidence of an Interaction between Sleep Abnormalities and Disruption of Circadian Rhythms of (a) Cytokines, (b) Hormones of the HPA Axis, (c) GH, and (d) Melatonin in CFS and in Disorders Characterized by Symptoms Common in CFS?**

Sleep abnormalities have been described and documented objectively in a few polysomnographic studies in persons with CFS and fibromyalgia. Some investigators have suggested that sleep disturbances contribute significantly to the development of daytime fatigue and other related symptoms experienced by these people. In disorders of excessive daytime sleepiness and fatigue, such as sleep apnea and narcolepsy, as well as in experimental induction of sleepiness after a night of sleep deprivation, increased plasma concentrations of IL-6 and TNF- $\alpha$  have been reported. In addition, situations associated with poor sleep and fatigue, such as insomnia or old age, are associated with a 24-hour hypercortisolemia and a circadian alteration of cytokine secretion, i.e. a shift of the peak of IL-6 secretion from nighttime to daytime. The

exact sources of circulating IL-6 are unknown; however, it has been shown that adipose tissue produces IL-6 and that plasma IL-6 concentration correlates positively with body mass index – a measure of total body adiposity, suggesting that adipose tissue may be a major source of circulating IL-6.

Most studies of persons with fibromyalgia have demonstrated increased wakefulness and light sleep and decreased deep sleep. In the same studies a correlation was shown between the degree of sleep disturbance and the number of tender trigger points. However, no studies as yet have examined the association between HPA axis alterations and cytokine secretory patterns and sleep abnormalities in persons with fibromyalgia or CFS.

In studies of the same cohort of persons with fibromyalgia, GH and prolactin secretion was found to be decreased, particularly in the first half of the night. One limitation of this study was the absence of frequent samples throughout the 24-hour sleep-wake period. One study showed that patients with CFS had a low nocturnal GH secretion, even though the IGF-1 serum levels were normal.

The role of melatonin in sleep pathophysiology in CFS is unclear. One study indicated that nocturnal melatonin secretion was elevated in persons with CFS. On the other hand, two studies have shown that melatonin is not effective in the treatment of sleep disturbances in persons with CFS, including adolescents.

No other studies have shown how treating the sleep disturbances in CFS will affect the overall symptomatology of CFS. Some physicians report improvement in sleep disturbance with small doses of tricyclic antidepressants. The effects of different degrees of physical activity on sleep have not been studied.

### **Question 5: Is There a Link between the Neuroendocrine Profile in Depression (Melancholic and/or Atypical) and CFS?**

There are symptoms common among persons with CFS, depression, fibromyalgia, and related syndromes. These symptoms include fatigue, cognitive impairments including difficulty concentrating, and sleep disturbances. The best-studied syndrome from a neuroendocrine standpoint has been major depression. Studies dating to the early 1970s have consistently shown that a substantial percentage (25–90%) of persons with various types of major depression have excessive activity of the HPA axis. These HPA axis abnormalities have been consistently

described in depressed persons with melancholic features. Other investigators have also reported that HPA axis activity may be diminished in depressed persons with atypical features when compared with persons with melancholic features. Other findings in melancholic depression have included abnormalities in the feed-forward and feedback loops of the HPA axis; blunted ACTH response to CRH infusion; heightened cortisol response to ACTH and ovine CRH infusion; early escape of cortisol suppression after dexamethasone suppression; heightened adrenocortical ACTH receptor sensitivity, and increased adrenal gland volume.

In part, these HPA axis disturbances have been attributed to dysregulation in the central stress-immunoendocrine-mediated response.

In related syndromes like CFS and fibromyalgia, a stress-induced immunoendocrine disturbance has also been hypothesized. However, in contrast to the consistent finding of HPA axis activation in melancholic depression, basal and dynamic studies of the HPA axis in persons with CFS have been contradictory. In depression, increased CSF levels of CRH have been found, while in CFS, CRH levels have been reported to be normal or even low. Several preliminary studies in CFS have shown a blunted ACTH response to CRH, similar to that seen in major depression. Finally, persons with CFS demonstrated a diminished cortisol response to synthetic ACTH infusions compared to persons with major depression. These data indicate potentially contrasting neuroendocrine responses and may point toward a putative biological marker for persons with CFS compared to persons with depression. Moreover, these findings may reflect how stress leads to different outcomes in persons with syndromes sharing some symptoms, such as CFS, major depression, or irritable bowel syndrome.

In addition to ACTH and cortisol disturbances in persons with CFS and major depression, other neuroendocrine parameters have been examined in these disorders and found to be abnormal. For example, shifts in diurnal patterns of behavior, temperature sensitivity, and hormone patterns have been well documented in persons with major depression, but have been less characterized in individuals with CFS and related disorders.

## Question 6

### (a) *What Are the Recommendations for Future Research?*

Numerous studies of adult, adolescent, and child populations, utilizing different study designs are necessary to address the diversity of questions for future CFS research. Recommendations are presented in two parts, the first addressing study designs that would address critical questions, and the second, addressing areas of research that warrant investigation.

#### Part I: Study Design Recommendations

*Prospective Studies.* Prospective (cohort) studies are needed to evaluate the specific stressors that have previously been hypothesized to cause CFS. For example, an infectious etiology could be studied by following over time a group of individuals who have had a protracted viral illness. Similarly a trauma stressor hypothesis might be examined by studying groups of individuals exposed and unexposed to major or minor trauma.

In addition, most studies of CFS etiology focus on determining associations between selected risk factors and prevalent disease. Patients included in these studies have usually been ill for a long period of time (median 5–6 years). Comorbidities thus cloud the clinical picture. Furthermore, chronic illness of any etiology can lead to abnormalities of the immune-neuroendocrine system, rendering such studies more difficult to interpret. Thus, prospective studies need to be conducted to determine factors associated with incident (i.e. new-onset) CFS; such studies will potentially shed light to the etiology of CFS.

*Studies of the Natural Course of CFS.* Longitudinal studies should be undertaken to better characterize the fluctuation in the clinical course of CFS.

*Intervention Studies.* Intervention studies are needed due to the paucity of published treatment data. These interventions might include certain antidepressant medications, immunomodulating agents, and drugs that may affect HPA axis activity, catecholamines, or indolamines. In addition, studies of the benefits and limitations of psychotherapy or physical therapy interventions in persons with CFS should be considered. The development of long-acting agonist and antagonistic CRH analogs may provide useful probes for studying HPA axis function in CFS, and may lead to treatment interventions for this disorder. Other specific receptor-based agents that might affect catecholamines, serotonin, and other neurotransmitter systems may provide additional treatment interventions for CFS.

*Case-Control Studies.* Refinement of the design and implementation of early research on CFS and related disorders is clearly warranted. In particular, more extensive case-control studies should be undertaken in order to differentiate possible subtypes of persons with CFS. For instance, some investigators have found enhanced HPA axis activity in individuals with CFS, while others have reported normal or even low HPA axis activity in individuals with CFS. Thus, closer attention to neuroendocrine activity in larger populations of people with CFS and related disorders will help to differentiate those who have hyperactivity of the HPA axis from those who do not. These could represent syndromal subtypes of CFS.

*Human Models.* Another suggested research paradigm is the development of human experimental models that could temporarily recreate the symptoms of CFS. This would permit identification of potential behavioral or biomarkers. For example, some investigators have suggested the brief administration of cytokines that induce short-term fatigue and sleep disorders (e.g., IL-6), as models for CFS. Another example might be the development of an exercise model of CFS in which healthy subjects engage in intense exercise for a period of time, which is then abruptly discontinued. Preliminary data have suggested that cessation of exercise may produce temporary alterations in HPA axis, autonomic, and cytokine regulation.

CFS symptoms are reported by some women with CFS to remit during pregnancy. Since pregnancy is associated with multiple profound hormone changes, it is possible that administration of the hormones associated with pregnancy might be of benefit in this syndrome. In order to further evaluate the role of pregnancy hormones in the pathogenesis of CFS, it would be important to study women with CFS who become pregnant in order to identify a time at which the symptoms are alleviated and the corresponding hormonal profile at that time. Hormones that are elevated at that time would be candidates for therapy of the syndrome. Pregnancy is associated with a massive increase in plasma human chorionic gonadotropin and elevations in estrogen, progesterone, and many other hormones produced by the placenta, such a placental lactogen. There is an elevation of plasma cortisol in the third trimester of pregnancy, and therefore, it is crucial to find out at what time during pregnancy symptoms are ameliorated and the hormonal profile at that time. Since there is already some evidence that cortisol may be involved in the symptomatology, it would be particularly interesting to determine whether or not the elevation in cortisol associated with pregnancy is associated with the amelioration.

Pregnancy is a human model for the treatment of CFS and could provide a very valuable tool to develop an effective treatment for the syndrome.

## Part II: Research Topic Recommendations

Because CFS and related disorders such as fibromyalgia, OI, and others may be more common in women, future studies in these areas should also focus on the significance of menarche, the menstrual cycle, pregnancy, menopause, and other gender-specific issues across the female life cycle. Additional studies of special populations such as children and adolescents should be undertaken.

Both estradiol and progesterone have cognitive, behavioral and psychological effects. A recent study reported a higher frequency of disorders of the hypothalamo-pituitary-gonadal (HPG) axis in women with CFS. Additional studies focusing on the role of abnormalities of the HPG axis – including menstrual cycle irregularities – on the symptomatology of CFS should be undertaken. In recent years the role of androgens in female physiology has been emphasized as evidenced by the addition of testosterone in many hormone replacement regimens after menopause. The few studies that have addressed the issue of circulating androgens in patients with CFS have yielded conflicting results. Thus, further well-controlled studies with larger sample sizes are needed to elucidate the role of androgens in the pathophysiology of CFS. The postpartum state bears many similarities to CFS (examples include immune activation and fatigue), and is associated with certain syndromes, such as postpartum thyroiditis and postpartum depression. Studies focusing on mood, cognition, sleep physiology, and fatigability in the postpartum period can potentially shed some light on the role of reproductive hormones, glucocorticoids, and certain neuropeptides in the clinical manifestations of CFS. Additional studies of special populations such as children and adolescents should be undertaken.

Polysomnographic studies of CFS should focus on the relationship between sleep disturbance, daytime fatigue, varied levels of physical activity, and alterations in pain threshold.

### *(b) What Are the Recommended Opportunities for Research Collaboration?*

It should be emphasized that CFS is a systemic illness characterized by dysregulation in a number of highly integrated modulatory systems. Thus, future research efforts should apply an integrative approach toward elucidating the etiology and other determinants of this disorder. Furthermore, the early recognition and treatment interven-

tion of individuals with CFS may result in important naturalistic studies on the course of this recurrent and disabling disorder.

CFS provides an ideal medium for fostering exciting research collaborations in what might appear to be unrelated disciplines. For example, the integration of research findings in areas as divergent as cardiovascular physiology, neuroendocrinology, immunology, infectious disease, psychiatry, sleep physiology, epidemiology, and genetics. Heretofore, CFS research has been largely limited to research within single disciplines. Cross-pollination of ideas and the formation of multidisciplinary teams would result in a fertile and far-reaching approach to elucidate the pathophysiology and treatment of this disorder.

### *(c) What Methodological Barriers Are There to the Careful Study of These Recommendations?*

(1) All of the study design and research topic recommendations presented are dependent on an adequate supply of subjects who have been properly diagnosed with CFS. CFS is an especially challenging diagnosis to make with confidence. In the absence of a diagnostic marker, it remains a diagnosis requiring astute clinical perception and careful exclusion of other illness states. Recent population-based studies have suggested that CFS is vastly underrecognized and underdiagnosed. For example, two extensive telephone surveys (CDC and DePaul University) reported that more than 85% of individuals who met the international case definition for CFS were never diagnosed or treated.

Better education of primary care and specialty care providers regarding the detection, diagnosis, and management of CFS is vital. In addition to identifying a rich source of clinical subjects for research studies in this area, increased recognition of CFS by health care professionals would promote earlier, and possibly more effective, diagnosis and treatment, resulting in better patient outcomes. Earlier diagnosis of cases would also be particularly meaningful for conducting etiological, prospective, longitudinal, and intervention studies.

(2) The diagnostic nosology of CFS is fluid. The international research case definition for CFS, first published in 1988, was revised in 1994 to facilitate a more standardized method of data collection. However, some of the case definition criteria are still subjective and difficult to operationalize. For example, the terms ‘substantially’ in ‘fatigue that is not substantially alleviated by rest’, or ‘lifelong’ in ‘fatigue that has not been lifelong’, or ‘exertional’ in ‘postexertional malaise lasting more than 24 h’ are open to the investigator’s interpretation. These interpre-

tations can lead to confusion in syndromal recognition and create overlap with related and unrelated medical and neuropsychiatric disorders. This barrier can be overcome when more objective and discriminating biological markers are identified and incorporated into the research case definition.

(3) In addition to the foregoing, the clinical symptomatology and illness progression may vary widely among individuals with CFS. In some, the syndrome may have a chronic, unremitting course, while in others, it may be more episodic and characterized by periods of remission and exacerbation. This diversity of clinical presentation, along with the presence of other, comorbid medical and neuropsychiatric disorders, may result in a heterogeneous patient study population. Therefore, longitudinal studies are recommended to capture fluctuations in the clinical course of CFS and related disorders. When sample sizes are large enough to allow for stratification, subgroup analyses must be performed. Factors of interest are onset type (sudden vs. gradual), types of comorbidities (fibromyalgia, major depressive disorder, primary sleep disorders), duration of illness (short vs. long), cognitive impairment, documented infection, severity of illness, functional status, current body mass index, or change in body mass index since onset. Finally, persons with CFS should be subdivided according to the presence or absence of neuroendocrine abnormalities such as HPA axis abnormalities, autonomic nervous system abnormalities, and sleep abnormalities, and studied independently and/or in comparison with one another. This will help identify and understand pathophysiologic mechanisms leading to distinct subtypes of CFS.

(4) Barriers to identifying these subtypes may be the result of inappropriate choice of control groups, failure to adequately account for confounding factors in the study design and analyses, and inefficient use of statistical techniques. Thus, it is recommended that an attempt be made to choose controls that are representative of the same population in which cases arise, that matched studies and subsequent matched analyses be undertaken to improve the efficiency of the estimated parameters, and that the most appropriate statistical tools including nonparametric statistics, stratification, and regression modeling be employed.

## Conclusions

Preliminary research has shown that HPA axis impairment likely plays a role in the pathophysiology of CFS, but the nature of the neuroendocrine abnormalities has not yet been clearly defined. It is likely that these abnormalities are related to the cytokine and autonomic nervous system abnormalities seen in CFS, as these systems influence and are influenced by one another. For example, cytokines implicated in CFS, such as TNF- $\alpha$  and IL-6, stimulate the HPA axis when the body is under stress or experiencing an infection. Excessive secretion of inflammatory cytokines such as TNF- $\alpha$  may induce OI. Additionally, sleep abnormalities, which are suspected to contribute to excess daytime somnolence in CFS, have been shown to be associated with increased production of IL-6 and TNF- $\alpha$ . Studies of the association between HPA axis abnormalities, cytokine secretion patterns, OI, and sleep abnormalities should be conducted in CFS.

Methodologic problems, such as the relapsing-remitting nature of the illness, the long illness duration of most study subjects, small sample sizes, and differences in research study designs, have hampered efforts to better understand neuroendocrine abnormalities. Longitudinal studies are needed to capture the illness fluctuations; human and animal experimental models could help identify potential biological markers; intervention studies would improve patient care and provide clues to the pathophysiology of CFS; prospective studies would evaluate suspected risk factors and etiologies, and large population studies would evaluate neuroendocrine activity in larger populations of persons with CFS, including those that fit specific subtypes of the disease.

Because CFS is a complex, multisystemic condition, novel research approaches must be employed. The formation of collaborative, multidisciplinary research groups developing and executing methodologically sound studies will provide the greatest opportunity for advancing research and understanding of this debilitating condition.

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