EDITORIAL

Chronic Fatigue Syndrome: The Need for an Integrative Approach

The syndromal presentation of chronic fatigue, feverishness, diffuse pains and other constitutional complaints, often precipitated by an acute infectious illness and aggravated by physical and emotional stressors, has a lengthy history. It has been described in the medical literature since the early 1700's. Sir Richard Manningham wrote, in 1750, of the 'febricula' or 'little fever' which presented with a variety of constitutional complaints, but few objective clinical findings (Manningham 1750). One of the more lasting appellations for this cluster of symptoms, 'neurasthenia,' was introduced by George Beard in the late 19th century, and is still used today in the 9th Revision of the World Health Organization's International Classification of Diseases (Beard 1869). Beard maintained that the etiology of this syndrome resided in subtle and undetectable alterations in neurochemistry, but the pathophysiology remains unknown more than a century later. Recent investigators have emphasized its heterogeneity, the multiple terms used to describe the syndrome, and its possible connections to other proposed entities such as fibromyalgia (Straus 1988a; Swartz 1988). The situation remains confusing.

To facilitate identification of objective characteristics and improve comparability of research studies, the Centers for Disease Control recently proposed a working case definition, renaming the illness "chronic fatigue syndrome" (Holmes et al 1988). Essentially, patients meeting criteria for the syndrome must have persistent or relapsing, debilitating fatigue for at least six months in the absence of any apparent medical diagnosis which would explain the clinical presentation. The CDC symptom criteria for this syndrome are presented in Table 1.

Two principal theories have dominated pathophysiologic concepts of this syndrome. One view has focused on the behavioral antecedents of the illness and maintains that this disorder represents the behavioral aftermath of an acute infectious event in psychologically susceptible individuals. In 1941, Paul Wood wrote, ". . . patients should be informed of the nature of their illness and be treated as psychoneurotics; their distaste for this label may prove quite helpful. . . The patient must be induced to believe that he is suffering from the effects of emotional disturbance and not from any disease or alteration of visceral function . . ." (Wood 1941). An alternate view has emphasized the importance of the infectious onset, with the protean constitutional symptoms emerging secondary to persistent immune activation and/or other lasting pathophysiologic changes caused by the initial infectious event. Inadequate attention has been given to how these two views might interface.

A number of early studies served to bolster the 'behavioral' viewpoint noted above. In 1951, Spink studied 65 patients with documented acute brucella infection, and noted that approximately 20 per cent of these patients proceeded to have prolonged symptoms without any objective evidence of continued active disease (Spink 1951). He observed a high degree of psychological morbidity in this subgroup of patients, and speculated that, ". . . individuals with functional complaints or personality difficulties may have an ex-

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Table 1. Centers for Disease Control (CDC) Case Criteria for Chronic Fatigue Syndrome

Major Criteria: (Patient must fulfill major criteria 1 and 2)

1) New onset of persistent or relapsing, debilitating fatigue or easy fatigability that does not resolve with bedrest and is severe enough to impair average daily activity below 50% of premorbid activity level, lasting for a period of at least 6 months.
2) Exclusion of other clinical conditions or medication effects by appropriate history, physical examination or laboratory tests.

Minor Critera: (Patient must show 6 or more of the symptom criteria and 2 or more of the physical criteria; or 8 or more of the symptom criteria)
Symptom criteria (must have begun at or after onset of the fatigue and must be persistent or recurring):

1) Mild fever or chills
2) Sore throat
3) Painful anterior or posterior cervical or axillary lymph nodes
4) Generalized muscle weakness
5) Myalgias
6) Prolonged post-exertional fatigue
7) Headaches
8) Migratory arthralgia
9) Neuropsychologic complaints (incl., photophobia, transient scotomata, forgetfulness, irritability, confusion, depression, poor concentration)
10) Sleep disturbance
11) Main symptom complex having an abrupt onset

Physical criteria: (must be documented on at least two occasions, at least one month apart)

1) Low grade fever (oral T 37.6–38.6°C or rectal T 37.8–38.8°C)
2) Nonexudative pharyngitis
3) Palpable anterior or posterior cervical or axillary lymph nodes

aggeration of these manifestations following acute brucellosis. . . ." Using more formalized psychological and medical assessments, Imboden and Cluff, at Johns Hopkins University, arrived at a similar conclusion (Imboden et al 1959). They summarized that chronic brucellosis, ". . . consists mostly of an emotional disorder. . . ." Reasoning that the factors involved in the delay of symptomatic recovery from acute brucellosis might be applicable to other acute infections, Imboden and Cluff designed a prospective psychological evaluation of 600 individuals prior to the onset of the expected nationwide epidemic of Asian influenza in 1957 (Imboden 1961). Twenty-six individuals developed the influenza syndrome; 12 had symptoms that persisted beyond three weeks. Their prospective evaluation confirmed that patients in the persistently ill group showed uniformly higher levels of pre-illness psychological distress. Recently published studies using structured psychiatric interview techniques have also suggested that the prevalence of psychiatric illness was higher in patients with chronic fatigue syndrome than in the general population, and often preceded the onset of the fatigue syndrome (Taerk et al 1987; Manu et al 1988; Manu et al 1989; Kruesi et al 1989; Gold et al 1990). Only one study reported the prevalence of psychiatric illness to be comparable to that of the general population, and to follow, rather than precede the development of the chronic fatigue (Hickie et al 1990). However, lacking reliable biological measures to identify this syndrome, and given that most established psychiatric diagnostic systems include fatigue as a symptom of psychiatric disorder, the use of phenomenologic criteria alone introduces an unavoidable circularity of reasoning when trying to establish a definitive distinction between chronic fatigue and a psychiatric illness.

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Evidence supporting an infectious or persistent immune dysregulation hypothesis for the pathophysiology of chronic fatigue has largely emerged from a series of reports which began appearing between 1982 and 1985. These studies reported a spectrum of subtle abnormalities in cell-mediated and humoral immunity in these patients, along with atypical profiles of antibody responses to the Epstein-Barr virus and other viral antigens (Tobi et al 1982; Jones et al 1985; Straus et al 1985). These immunologic disturbances, coupled with the clinical observation that many of these patients developed the syndrome following an episode of acute infectious mononucleosis, led to the specific hypothesis that the illness was a manifestation of chronic Epstein-Barr virus infection. However, several subsequent observations challenge this idea and suggest that, while immune activation may be present in these patients, *persistent* Epstein-Barr virus infection is almost certainly not a tenable explanation for most cases of the syndrome. First, the magnitude or pattern of the antibody titers bears no relationship to the severity of the clinical presentation. Furthermore, controlled studies of seroepidemiology showed that enhanced activity of the Epstein-Barr virus may persist for as long as 30–104 months after the acute infection in otherwise asymptomatic individuals (Horwitz et al 1985; Holmes et al 1987; Buchwald et al 1987). Finally, a controlled trial of intravenous and oral acyclovir was without effect in patients with chronic fatigue syndrome (Straus et al 1988b). Nevertheless, a role for persistent pathophysiologic changes following an acute viral infection, has not been excluded as a possible pathogenesis of chronic fatigue syndrome. Indeed, Oldstone and colleagues, have provided evidence in animals demonstrating that viral infections may lead to long-lasting pathologic changes in differentiated cellular functions, long after the infection itself has resolved (Oldstone et al 1982). This process may result in substantial disturbances in organismic homeostasis, without damaging the morphologic appearance of the infected cells.

Despite the prominence of central nervous system symptoms in these patients, remarkably few studies of this syndrome have involved investigators skilled in psychiatry. The lack of such involvement has consistently impaired an integrative understanding of this syndrome, limited the development of new pathophysiologic models, perpetuated the stigma associated with behavioral symptoms, and fostered methodologic problems in research. At the present time, a scientific bias in research in this area persists in the form of a search for a specific, infection-produced disturbance in immune function. This is the case despite the fact that there exists little evidence to suggest that the observed mild immune abnormalities are of any functional significance. Psychiatrically ill comparison groups have been virtually absent, with one important exception (Wessely, Powell 1989). In their study, Wessely and Powell conclude that the description of fatigue in patients with "postviral" fatigue syndrome more closely resembled a comparison group of affectively ill patients than a group of patients with primary neuromuscular disorders. However, they emphasize that depression alone cannot be the sole explanation for the similarity in phenomenologic presentation. Nearly one third of all patients with "postviral" fatigue had no diagnosable psychiatric disorder. In their words, "[chronic fatigue syndrome] is a heterogenous condition, depressive illness is a sufficient, but not necessary, explanation. . . ."

An interdisciplinary approach to studies in this area is advocated; psychiatry should be a primary component of such an approach. It is ironic that most non-psychiatric researchers in this field have long acknowledged the need for such involvement. For instance, a formal structured psychiatric interview is now considered to be an essential component of a credible research workup for chronic fatigue syndrome. These issues

were discussed in detail at a recent workshop on the Definition and Medical Outcome Assessment of Chronic Fatigue Syndrome in Research, sponsored jointly by the National Institute of Mental Health and the National Institute for Allergy and Infectious Diseases. This commendable joint effort represented the first formal involvement of the NIMH in this area.

To begin exploring potential biological underpinnings of the clinical common ground between chronic fatigue syndrome and primary psychiatric illness, we recently advanced data suggesting that the phenomenologic overlap may reflect the occurrence of a shared, final common biological pathway that may be precipitated by a variety of infectious or non-infectious pathophysiologic antecedents (Demitrack et al 1991). Several lines of evidence implicate disturbances in the hypothalamic-pituitary-adrenal axis as this shared final pathway. First, a review of the clinical presentation of chronic fatigue syndrome shows considerable overlap with that seen in patients with glucocorticoid deficiency (Baxter et al 1981). Indeed, one of the principal symptoms of glucocorticoid deficiency is debilitating fatigue. An abrupt onset precipitated by a stressor, feverishness, arthralgias, myalgias, adenopathy, postexertional fatigue, exacerbation of allergic responses, and disturbances in mood and sleep are also characteristic of glucocorticoid insufficiency. Notably, these symptoms are often seen in the relatively rare syndrome of partial or subclinical adrenal insufficiency, which may only be detectable by ACTH stimulation or other endocrine testing in patients who fail to show the symptoms of classical Addison's disease, such as hypotension and abnormal fluid and electrolyte balance. Since glucocorticoids represent the most potent endogenous immunosuppressive agents, we further suggest that many of the observed immunologic disturbances in patients with chronic fatigue syndrome (e.g., exacerbation of allergic responses, and the profile of enhanced antibody titers to a variety of viral antigens) could also reflect a mild glucocorticoid deficiency. In this regard, it has recently been shown in animals that a defect in the responsiveness of the hypothalamic-pituitary-adrenal axis to immune mediators confers a risk for the development of inflammatory disease (Sternberg et al 1989a; Sternberg et al 1989b).

A second line of evidence implicating disturbances in the functional integrity of the hypothalamic-pituitary-adrenal axis focuses upon corticotropin-releasing hormone. Other clinical populations with similar behavioral features characterized by profound lethargy, fatigue and depressed mood (often referred to as 'atypical' depressive syndromes), may show evidence of hypofunctioning of hypothalamic corticotropin-releasing hormone neurons. These illnesses include Cushing's disease (Kling et al 1991; Tomori et al 1983), hypothyroidism (Kamilaris et al 1987), and the depressed phase of seasonal affective disorder (Joseph-Vanderpool et al 1991). These findings are of interest because corticotropin-releasing hormone serves not only as the principal stimulus to the pituitary-adrenal axis, and hence could be involved in cases of subtle adrenal insufficiency, but also because it is a behaviorally-active neurohormone whose central administration to animals and non-human primates induces signs of physiological and behavioral arousal, including activation of the sympathetic nervous system (Brown et al 1982), hyperresponsiveness to sensory stimuli (Swerdlow et al 1986), and increased locomotion (Sutton et al 1982). Hence, a functional deficit of hypothalamic corticotropin-releasing hormone could contribute to the profound lethargy and fatigue that are inherent characteristics of both 'atypical' depressive syndromes and chronic fatigue syndrome, either through direct effects upon the central nervous system or indirectly by causing glucocorticoid deficiency. In summary, we have hypothesized that a variety of infectious or non-infectious patho-

physiologic antecedents may lead to a specific neuroendocrine deficit, namely, a reduction in adrenal glucocorticoid secretion mediated by an impairment in the central nervous system regulation of the axis. This pattern of secondary adrenal insufficiency, in turn, may be a consequence of as well as a causative factor in the development of many of the behavioral and biochemical abnormalities that have been described in patients with chronic fatigue syndrome. Similarly, other clinical states, with widely differing pathophysiologies, may result in a fatigue-like syndrome due to a functional deficit in hypothalamic corticotropin-releasing hormone.

The validity of this model remains to be determined. Of greatest importance, available data indicate that as investigators evaluate this model, or any other, an integrated, interdisciplinary perspective is crucial. Characteristics essential to such an approach include thorough psychiatric assessments using standardized instruments with demonstrated reliability and validity, comparative analyses employing clearly defined psychiatric populations, and neurobiological models which address the interaction of brain and behavior in the clinical expression of this illness.

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