Neuropsychology Review, Vol. 15, No. 1, March 2005 (© 2005)
DOI: 10.1007/s11065-005-3588-2

Chronic Fatigue Syndrome: The Need for Subtypes

Leonard A. Jason,[1,4] Karina Corradi,[1] Susan Torres-Harding,[1] Renee R. Taylor,[2] and Caroline King[3]

Chronic fatigue syndrome (CFS) is an important condition confronting patients, clinicians, and researchers. This article provides information concerning the need for appropriate diagnosis of CFS subtypes. We first review findings suggesting that CFS is best conceptualized as a separate diagnostic entity rather than as part of a unitary model of functional somatic distress. Next, research involving the case definitions of CFS is reviewed. Findings suggest that whether a broad or more conservative case definition is employed, and whether clinic or community samples are recruited, these decisions will have a major influence in the types of patients selected. Review of further findings suggests that subtyping individuals with CFS on sociodemographic, functional disability, viral, immune, neuroendocrine, neurology, autonomic, and genetic biomarkers can provide clarification for researchers and clinicians who encounter CFS' characteristically confusing heterogeneous symptom profiles. Treatment studies that incorporate subtypes might be particularly helpful in better understanding the pathophysiology of CFS. This review suggests that there is a need for greater diagnostic clarity, and this might be accomplished by subgroups that integrate multiple variables including those in cognitive, emotional, and biological domains.

KEY WORDS: chronic fatigue syndrome; subtypes; immunology; neuroendocrinology.

Chronic fatigue syndrome (CFS) is an incapacitating illness affecting approximately 800,000 Americans (Jason et al., 1999f), and the annual total value of lost productivity in the United States due to this illness has been estimated to be $9.1 billion (Reynolds et al., 2004). Individuals with CFS have been found to differ with respect to characteristics such as the case definition utilized, psychiatric comorbidity, method of case ascertainment, functional disability, and viral, immunologic, neuroendocrine, neurology, autonomic, and genetic biomarkers (Jason et al., 2003a). As a result of this heterogeneity, findings emerging from studies in a number of areas are, at best, discrepant, and at worst, contradictory. Heterogeneity among participant groups can also contribute to a lack of observable abnormalities in some laboratory studies (Friedberg and Jason, 1998). There probably are different types of illnesses now contained within the CFS construct, which makes it even more difficult to identify commonalities in people with this diagnosis. This article will review the various demographic and clinical variables associated with onset, clinical expression, and severity of CFS, and then provide hypotheses regarding the identification of subtypes that emerge from the previously defined correlates.

It is important to determine which case definition to use in defining the syndrome. The benefit of classifying patients into diagnostic categories is that it facilitates communication among clinicians and researchers, selection of treatment methods, and prediction of response to treatment (King and Jason, 2004). One of the greatest sources of diagnostic unreliability is criterion variance, differences in the formal inclusion and exclusion criteria used by clinicians to classify patients into diagnostic categories (Spitzer et al., 1975).

[1]DePaul University, Chicago, Illinois.
[2]University of Illinois at Chicago, Chicago, Illinois.
[3]Hines VA, Hines, Illinois.
[4]To whom correspondence should be addressed at DePaul University, Center for Community Research, 990 W. Fullerton Avenue, Chicago, Illinois 60614; e-mail: ljason@depaul.edu.

Which Case Definition to Use: Holmes, Fukuda, Canadian?

Currently, scientists throughout the world use the Fukuda et al. (1994) CFS case definition, which requires a person to experience six or more months of chronic fatigue of new or definite onset, that is not substantially alleviated by rest, not the result of ongoing exertion, and that results in substantial reductions in occupational, social, and personal activities. To be diagnosed with CFS, individuals also need to have the concurrent occurrence of four or more symptoms that did not predate the illness and persisted six or more months since onset (i.e., sore throat, lymph node pain, muscle pain, joint pain, postexertional malaise, headaches of a new or different type, memory and concentration difficulties, and unrefreshing sleep). The article by Fukuda et al. actually called for subgrouping within the identified group of individuals with CFS, thus suggesting an awareness that a heterogeneous group was being identified. Unlike the first CFS criteria published by Holmes et al. (1988) (as specified by the Schluederberg et al., 1992 revision), the presence of anxiety disorders, somatoform disorders, and nonpsychotic or nonmelancholic depression prior to CFS onset does not constitute exclusionary conditions under the Fukuda et al. (1994) definition. In addition, the Fukuda et al. criteria require the concurrent occurrence of at least four of eight symptoms (sore throat, muscle pain, etc.), as compared with eight or more required by the prior Holmes et al. (1988) CFS criteria. Jason et al. (2001e) compared the Fukuda and Holmes criteria and found that the Holmes criteria did select a group of patients with higher symptomatology and functional impairment.

More restrictive or more liberal criteria clearly have an effect on who is classified as having CFS but these different definitions also pose difficulties in interpreting results of related studies. For example, Komaroff and associates (1996) compared patients meeting the major criteria of the original U.S. CFS case definition (Holmes et al., 1988) with healthy controls and groups with multiple sclerosis and depression (91% of this sample met the CFS case definition). They concluded that eliminating muscle weakness, arthralgias, and sleep disturbance, and adding anorexia and nausea would strengthen the case definition. In contrast, using the Fukuda et al. (1994) criteria, Jason et al. (2002c) compared individuals with CFS, melancholic depression, and controls, and in contrast to the Komaroff study, muscle weakness and arthralgias were reported in over half of participants with CFS and uniquely differentiated this group from controls. Jason et al. (2002c) also found that anorexia and nausea occurred with relatively low frequency and neither symptom uniquely differentiated those with CFS from controls. Further, Jason et al. (2002c) found a symptom currently not part of the Fukuda criteria, shortness of breath, did differentiate the groups. This symptom might play a role in neurally mediated hypotension, which has been connected to CFS (Poole et al., 2000).

Efforts to develop a case definition can be traced back even earlier. In 1955, there was an outbreak of a CFS-like illness at the Royal Free Hospital, and Ramsay (1981, 1988), the medical consultant in charge, published a definition of this disease using the term Myalgic Encephalomyelitis (ME) (Hyde et al., 1992). The most prominent of the criteria include: (1) fatigue after minimal exertion (not daily fatigue) or delay of recovery of muscle power after exertion ends; (2) one or more symptoms that indicate circulatory impairment; (3) one or more symptoms that indicate central nervous system involvement (cerebral problems); (4) and fluctuating symptoms (Ramsay, 1981, 1988).

Dowsett and associates (1990) operationalized Ramsey's definition (ME) into criteria which bear some similarity to a case definition developed in Australia by Lloyd et al. (1990). Lloyd et al. stipulate that postexertional malaise, as well as memory and concentration difficulties, are central for a diagnosis. In contrast, for the Fukuda et al. (1994) criteria, these symptoms are optional as they represent only two symptoms among a group of eight, of which a patient must have four. To date, there has only been one investigation comparing the Fukuda et al. (1994) CFS criteria with the ME criteria (Jason et al., 2003b). Those meeting the ME criteria, in contrast to those meeting the CFS Fukuda et al. (1994) criteria, had significantly poorer neurological, neuropsychiatric, fatigue/weakness, and rheumatologic symptoms than those with chronic fatigue explained by psychiatric conditions.

Recently, a new clinical case definition for ME/CFS has been developed in Canada. The Canadian clinical case definition specifies that the illness needs to persist for at least 6 months (Carruthers et al., 2003). In addition, there must be a marked degree of new onset of unexplained, persistent, or recurrent physical or mental fatigue that substantially reduces activity level. Postexertional malaise must occur with loss of physical or mental stamina, rapid muscle or cognitive fatigability, usually with 24 hr or longer to recover. There also needs to be unrefreshing sleep or sleep quantity or rhythm disturbance, and a significant degree of arthralgia and/or myalgia (there are a small number of patients with no pain or sleep dysfunction and a diagnosis can only be given when these individuals have a classical case with an infectious illness onset). In addition, there need to be two

or more neurocognitive manifestations (e.g., confusion, impairment of concentration, and short-term memory). Finally, there needs to be at least one symptom from two of the following categories: autonomic manifestations (neurally mediated hypotension, light headedness), neuroendocrine manifestations (e.g., recurrent feelings of feverishness and cold extremities), and immune manifestations (e.g., recurrent sore throats). Recently, Jason et al. (2004) compared persons meeting the Canadian case definition, the Fukuda et al. (1994) criteria, and people experiencing chronic fatigue explained by psychiatric reasons. The Canadian criteria group, in contrast to the Fukuda criteria group, had more variables that significantly differentiated them from the psychiatric comparison group. The Canadian criteria selected cases with less psychiatric comorbidity, more physical functional impairment, and more fatigue/weakness, neuropsychiatric, and neurology symptoms.

Research has also been directed at attempting to better classify symptoms of individuals with chronic fatigue and CFS. For example, using factor analysis, Nisenbaum et al. (1998) found three correlated factors (fatigue-mood-cognition symptoms, flu-type symptoms, and visual impairment symptoms). In a later study, Nisenbaum et al. (2004) found three factors among a sample of 1,391 chronically fatigued subjects; the factors were musculoskeletal, infection, and cognition-mood-sleep. Friedberg et al. (2000) also found three factors (cognitive problems, flu-like symptoms, and neurological symptoms) in a sample of patients with CFS. A study by Jason et al. (2002a) used factor analysis to provide support for the existence of four distinct components of chronic fatigue. The four were: Lack of Energy (fatigue intensity), Physical Exertion (fatigue exacerbated by physical exertion), Cognitive Problems (difficulties with short-term memory, concentration, and information processing), and Fatigue and Rest (rest or sleep is not restorative). Results of the study by Jason et al. (2002a) were of theoretical importance because two of the primary dimensions of fatigue that emerged within the CFS-like group, postexertional fatigue and cognitive problems, corresponded closely with definitional criteria for CFS (Lloyd et al., 1990). Postexertional fatigue and cognitive problems are part of the major criteria for the Canadian case definition for ME/CFS (Carruthers et al., 2003). Postexertional fatigue and cognitive problems appear to represent primary dimensions of CFS.

A cluster analysis of the data mentioned above was performed to define a typology of chronic fatigue symptomatology (Jason and Taylor, 2002). With respect to CFS, findings suggested that a majority of individuals with moderate to severe symptoms can be accurately classified into two important subgroups: one distinguished by severe postexertional fatigue, and fatigue that is alleviated by rest and the other distinguished by severe overall symptomatology, severe postexertional fatigue, and fatigue that is not alleviated by rest. One key characteristic that distinguished the two clusters that contained almost all participants with CFS to another cluster that contained only one CFS participant, was markedly high severity of postexertional fatigue.

Results from this investigation highlight the relative importance of this symptom as a diagnostic marker for CFS, and point to the potential utility in designating postexertional fatigue as a major criteria for CFS in future attempts to define the syndrome. A second key characteristic, fatigue in relation to rest, distinguished individuals in two clusters that contained individuals with CFS, with those in one cluster differing most significantly from those in the second with respect to whether their fatigue was alleviated by rest. One of the major criteria for the current U.S. definition of CFS (Fukuda et al., 1994) requires that fatigue is not substantially alleviated by rest in order for an individual to receive a diagnosis. Findings from this investigation suggest that this criteria may be more accurately designated as one of the secondary criteria for CFS, so that it does not artificially exclude those with CFS who may experience some symptom relief with rest. This recommendation has recently been included into the guidelines for the CFS case definition (Reeves et al., 2003). A third result deserving of attention involves the finding for more severe cognitive problems in the clusters of patients with CFS versus the cluster with only one CFS patient. This finding highlights the importance of cognitive problems to the experience of CFS and supports the designation of cognitive problems as a major criteria, which it is for ME (Dowsett et al., 1994), the Canadian case definition for ME/CFS (Carruthers et al., 2003), and the Australian (Lloyd et al., 1990) criteria.

Based on the research reviewed in this section, we would encourage researchers to compare and contrast categories of patients meeting the Canadian Case definition and the Fukuda et al. (1994) criteria. In addition, the provision of standardized measures for assessment and scoring guidelines should reduce clinicians' difficulty with the criteria and their need to modify the criteria in clinical practice. In effect, the use of standardized measures should reduce criterion variance and improve diagnostic reliability (King and Jason, 2004).

Unitary vs. Separate Diagnostic Entities

Before examining the literature on subtypes, it is first important to decide whether or not syndromes such as

CFS, Fibromyalgia (FM), and Irritable Bowel Syndrome (IBS) are best understood in terms of a unitary model of functional somatic distress or as separate diagnostic entities (Barsky and Borus, 1999). As an example of this type of research, Sullivan et al. (2002) used latent class analysis with 32 symptoms of patients with CFS, FM and CFS, and FM, and the findings supported the notion that CFS and FM have more similarities than differences. However, these investigators deliberately removed the major criteria symptoms (i.e., fatigue, widespread pain) for both syndromes before conducting the analyses, and the removal of these critical symptoms probably influenced the outcomes. In contrast, a study by Taylor et al. (2001b) evaluated the diagnostic validity of conditions that have been labeled functional somatic syndromes. Latent variable models of functional somatic distress were estimated from the responses of 213 community members to a medical questionnaire and the items that closely conformed to formal diagnostic criteria for the conditions were used in model estimation. Results of confirmatory factor analysis supported diagnostic distinctions between five syndromes (FM, CFS, somatic depression, somatic anxiety, and IBS). Discrete diagnostic categories of FM and CFS were then tested using logistic regression analysis, in which the outcome involved independent diagnosis of these conditions based upon physician evaluation. The diagnostic validity of the latent constructs of FM and CFS emerging from this five-factor model were cross-validated using findings from an independent physician evaluation.

Linder et al. (2002) used artificial neural networks to classify patients with chronic fatigue (including CFS and idiopathic chronic fatigue), lupus erythematosus, and FM. They were able to achieve a sensitivity of 95% and a specificity of 85%. Those chronic fatigue symptoms that had the highest accuracy were "acute onset of symptoms" and "sore throat," which supports the hypothesis of an infectious etiology. In further support of findings for distinctions among these syndrome constructs, Hickie and associates (1999b) found that chronic fatigue is a persistent diagnosis over time and that longitudinal patterns of comorbidity of fatigue with psychological distress did not suggest a causal relationship or common vulnerability factor. Similar findings from a study by Van Der Linden and associates (1999) supported the existence of a pure, independent fatigue state over time, with this pure fatigue state not predicting subsequent psychiatric disorder.

THE NEED FOR SUBGROUPS

Many efforts have been undertaken to subgroup patients with CFS. However, to date, no one method has proven to be consistently superior in differentiating subgroups or in suggesting treatment approaches more appropriate for individuals with similar disease presentation. Below we will review some of the more promising research in the area of subtyping and ultimately designate several categories and dimensions that might guide future research.

CFS vs. CFS Plus Psychiatric Comorbidity

In an influential review article, David et al. (1991) concluded that depression occurs in about 50% of CFS cases, while anxiety and other disorders (i.e., somatization, minor depression, phobia, anxiety disorders) occur in about 25% of cases. These findings have led some to conclude that CFS is solely a psychiatric disorder. Clauw and Chrousos (1997) argue that the inability of science to identify the precise physiologic basis for CFS should not lead to labeling an individual with CFS as having a psychiatric disorder, and in fact, this dualistic thinking about diseases as being either psychiatric or medical should probably be abandoned.

The Diagnostic Interview Schedule (DIS) (Robins et al., 1989), a structured psychiatric instrument designed for use in community surveys (Robins and Regier, 1991), has frequently been used to assess psychiatric comorbidity in CFS samples. However, this instrument was not designed for use with medically ill populations. By contrast, the Structured Clinical Interview for the DSM-IV (SCID) (Spitzer et al., 1995) uses open-ended questions and all potential sources of information to encourage a thorough description of the problems by the interviewee. Use of the SCID is also limited to highly trained clinicians more able to recognize the subtle distinctions between CFS and psychiatric disorders. A study by Taylor and Jason (1998) involved the administration of both the DIS and the SCID to a sample of patients with CFS. Of individuals diagnosed with CFS, 50% received a current Axis I psychiatric diagnosis when using the DIS, but only 22% received a current diagnosis when using the SCID. These findings suggest that high or low psychiatric rates in CFS samples may be a function of whether symptoms are attributed to psychiatric or nonpsychiatric causation.

The Fukuda et al. (1994) criteria do not explicitly exclude people who have purely psychosocial, stress, or psychiatric reasons for their fatigue. However, this broadening of the CFS definition raises questions regarding the extent to which patients with purely psychiatric explanations are erroneously included within the CFS rubric. Some individuals with CFS might have had psychiatric problems before and/or after CFS onset and yet, other

individuals may only have primary psychiatric disorders with prominent somatic features. Including the latter type of patients in the current CFS case definition could confound the interpretation of epidemiologic and treatment studies. Major Depressive Disorder (MDD) is an example of a primary psychiatric disorder that has some overlapping symptoms with CFS.

Fatigue, sleep disturbances, and poor concentration occur in both depression and CFS. It is important to differentiate those with a principal diagnosis of MDD from those with CFS only. This is particularly important because it is possible that some patients with MDD also have chronic fatigue and four minor symptoms that can occur with depression (e.g. unrefreshing sleep, joint pain, muscle pain, impairment in concentration). Fatigue and these four minor symptoms are also defining criteria for CFS. Is it possible that some patients with a primary affective disorder could be misdiagnosed as having CFS? Some CFS investigators would not see this as a problem because they believe that high rates of psychiatric comorbidity indicate that CFS is mainly a psychiatric disorder and that distinctions between the two phenomena are superficial and merely a matter of nomenclature.

However, several CFS symptoms, including prolonged fatigue after physical exertion, night sweats, sore throats, and swollen lymph nodes, are not commonly found in depression. In addition, while fatigue is the principal feature of CFS, fatigue does not assume equal prominence in depression (Friedberg and Jason, 1998; Komaroff et al., 1996). Moreover, illness onset with CFS is often sudden, occurring over a few hours or days, whereas primary depression generally shows a more gradual onset. Individuals with CFS can also be differentiated from those with depression by recordings of skin temperature levels and electrodermal activity (Pazderka-Robinson et al., 2004). In summary, CFS and depression are two distinct disorders, although they share a number of common symptoms. Most importantly, the erroneous inclusion of people with primary psychiatric conditions in CFS samples will have detrimental consequences for the interpretation of both epidemiologic and treatment efficacy findings.

Even after taking the above recommendations into consideration, some individuals with CFS will have a comorbid psychiatric condition, and it is important to correctly subclassify such individuals. Some medical illnesses (e.g., multiple sclerosis, hyperthyroidism) have been shown to elicit psychological disorders; changes in mood, fatigue, and malaise are commonly associated with infection (Ray, 1991). In addition, depression can be a reaction to physical illness. For example, depression and anxiety are common in patients with cancer and heart disease (Ray, 1991). Ray (1991) noted that depression that accompanies a prolonged illness may be better conceptualized as demoralization rather than as psychiatric illness, particularly in ambiguous illnesses in which patients have difficulty gaining recognition of the legitimacy of their illness.

Lange et al. (1999) found no MRI differences between those with CFS and healthy controls. However, when the CFS group was divided into those with and without a psychiatric disorder occurring since their CFS diagnosis, 66.7% of those without psychiatric comorbidity had MRI abnormalities vs. only 22.2% with psychiatric cormorbidity. The CFS without psychiatric diagnosis group had the highest frequency of MRI small, punctuate, subcortical white matter hyperintensities, abnormalities, which were most often found in the frontal lobes. Several studies have compared the functional status of patients with CFS having comorbid psychiatric conditions. In an important recent article, Tiersky et al. (2003) examined individuals with CFS with and without psychiatric comorbidity and they found that physical functional capacity was not worse in individuals with CFS and a concurrent psychiatric illness. Morriss and associates (1999) also found that depression was not associated with the reporting of pain, FM, IBS, and medically unexplained symptoms in individuals with CFS. Similarly, Ciccone et al. (2003) did not find that psychiatric illness, alone or in combination with a comorbid personality disorder, was associated with physical impairment. Even though it is unclear what the functional consequences are of having more lesions among CFS patients without psychiatric diagnoses, subtyping those with and without psychiatric comorbidity seems warranted.

Neurocognitive Functioning

As mentioned in a recent review chapter by DeLuca and Tiersky (2003), cognitive dysfunction is an important symptom of persons with CFS. Most individuals with CFS typically complain that fatigue affects their physical and mental functioning, and generally, they report problems with concentration and absentmindedness, including problems with impaired memory, difficulty making decisions, poor attention, difficulties taking in written or spoken material, and executing familiar sequences of events, such as grocery shopping (Wearden and Appleby, 1997). In addition, many patients with CFS complain that performing mental work is aversive for them, to the degree that they either stop doing it or start to experience symptoms (Wood et al., 1994). As a result, many people with CFS describe their cognitive difficulties as one of the

more disabling and troubling symptoms of their illness (Abbey and Garfinkel, 1991).

However, when people with CFS are administered a standard neuropsychological battery designed to screen for clinically significant deficits or abnormalities in cognitive functioning, they typically perform within the normal range on most tests, although overall performance may be slightly impaired (Wearden and Appleby, 1997). Higher cognitive functioning such as language, executive processes, and perceptual skills have not been found to be impaired in people with CFS (DeLuca and Tiersky, 2003; Grafman et al., 1993). No consistent or severe memory impairment is evident from the performance of people with CFS on neuropsychological tests (See DeLuca and Tiersky, 2003). Both verbal and visual free recall is unimpaired in people with CFS, however, some studies have found that people with CFS benefit less from cueing or context on memory tasks than healthy controls do (Moss-Morris et al., 1996). People with CFS have also been found to be more sensitive to interference and effort on memory tasks than would be expected from healthy controls. These memory impairments have been interpreted as a reflection of attentional rather than true memory deficits. Researchers have found that the way in which information is attended to and processed has a direct impact on the quality of the memory trace (Van Zomeren and Brouwer, 1994). Specifically, slowed processing has been found to limit elaboration of information during encoding. This finding helps explain why people with CFS have some trouble on tasks that rely on more complex effort, elaboration, or organization of material such as memorizing lists of words that are not semantically associated, or ordering sequences of responses in memory (Moss-Morris et al., 1996).

A number of explanations for the discrepancy between subjective reports of cognitive impairment and objective findings of cognitive impairments in people with CFS have been proposed. One explanation is that the complaints of people with CFS accurately reflect their everyday cognitive lapses, and that laboratory tests measure everyday cognitive functioning poorly. This explanation raises the question of how these subjective complaints are reflected in neuropsychological testing. Another explanation for this discrepancy is that when a patient undergoes cognitive testing in a clinic or a laboratory, motivation level and arousal level may be quite different from that in day-to-day life. Neuropsychological testing is critically dependant upon attention and arousal, and functions such as memory are closely related to general level alertness and physiological arousal (Wessely, 1993a,b). Thus, due to reactivity to the testing situation, people with CFS may actually perform better in laboratory settings. Finally, it has also been suggested that CFS patients may be able to perform normally but at the cost of extra effort that is often experienced as feelings of fatigue. A final word of caution regarding neuropsychological research in CFS is the tendency in many of these studies to use tasks that lack sufficient specificity to implicate any specific neuropsychological process such that the results could suggest that CFS patients were impaired across all tasks administered. Future studies should be based on a better understanding of the types of deficits that might be associated with CFS to avoid widespread testing of unrelated or unspecific constructs.

Despite the various and, at times, conflicting findings of neuropsychological studies examining cognitive functioning in CFS, some general trends can be extracted from these studies (Jason et al., 2000c). A consistent finding has been slower reaction times, poorer performances on complex attentional and memory tasks, and, less consistently, a slowness in acquisition of new information. Some CFS researchers have suggested that a single deficit, namely slower information processing may be responsible for all the impairments noted. However, more recent research suggests that slowed performance might be due to impaired motor processes rather than to problems with complex information processing (De Lange et al., 2004). Subtyping on whether or not patients have deficits on specific tasks (e.g., reaction times, motor processes, performance on complex attentional and memory tests) might help resolve many conflicting studies in this area.[5]

[5]The question then remains as how to best assess for symptoms of cognitive difficulty in patients with possible CFS during a diagnostic examination. Given that the majority of studies examining cognitive problems in patients with CFS revealed difficulties in memory and processing speed, it is recommended that clinicians primarily assess these two areas of cognitive functioning. For example, for patients reporting difficulty with memory or concentration, clinicians might ask the following series of follow-up questions: Do you have difficulty comprehending information? Does it take you longer to understand information? Do you have difficulty following information? Do you have to focus on one thing at a time? Do you frequently lose your train of thought? Do you have trouble expressing your thoughts? Do you speak the wrong words or make new words up? Do you have difficulty retaining information? Do you have difficulty recalling information? Do you frequently get words or numbers in the wrong order? In addition, all patients should be administered the 3-item recall measure from the Mini-Mental State Examination (Folstein et al., 1975) in which patients are given three words to recall after a brief period of time. Finally, it is recommended that a numerical rating of symptom intensity be obtained for reports of impaired memory and concentration (Jason et al., 2000). Some individuals might have more severe cognitive limitations and others more moderate and minor limitations, and this might provide researchers with another useful dimension for subtyping. Categorizing individuals into those with specific objective neuropsychological indicators versus those without them might also further research subtypes.

Community vs. Tertiary Care Recruitment

One central, methodological explanation for observations of discrepant findings across studies involves issues related to sampling and participant selection. A majority of investigations have employed nonrandom, medically-referred samples. Findings from several community-based studies are reviewed below to support the notion that the source of patient recruitment needs to be considered in CFS research. For example, in Great Britain, Pawlikowska et al. (1994) sought responses from 15,283 people in the general practice. Based on the Pawlikowska et al. (1994) sample, Wessely et al. (1995) later ascertained the presence of CFS in 1,199 people who presented to the physician with symptoms of infections and 1,167 who were seen for other reasons. Using health and fatigue questionnaires (Wessely et al., 1997), it was determined that 2.6% of the sample had CFS according to the Fukuda et al. (1994) criteria. It is of interest that these rates are within the range of prevalence of several mood disorders (the most prevalent psychiatric illness after anxiety disorders: for major depressive episode, the 1-month prevalence is 2.2%, and lifetime prevalence is 5.8%; Regier et al., 1988). These CFS prevalence rates are considerably higher than those reported in other CFS epidemiological studies.

In a subsequent study by Euba et al. (1996), those individuals with a CFS diagnosis in the community sample described above were compared with people diagnosed in a specialized CFS hospital unit. Whereas 74% of the community sample had a psychiatric diagnosis before the onset of their fatigue, only 21% of the hospital sample had a previous diagnosis. The community sample had significantly worse mental health scores and was more likely to encounter work-related impairment. Fifty-nine percent of the sample believed that their illness might be due to psychological or psychosocial causes (compared with 7% for the hospital sample). Wessely et al. (1997) did indicate that the 2.6% rate of CFS included both those with and without a psychiatric diagnosis, and if only those without a psychiatric diagnosis were counted, the CFS rate would be only 0.5%. Wessely et al. (1996) reported that of those 36 individuals who were diagnosed as having CFS from a cohort of 1,985 primary care patients, only 64% had sleep disturbances and 63% had postexertional malaise. These percentages are rather low, given that both symptoms are critical features of CFS. In addition, a linear relationship was found between functional impairment and psychological morbidity (Wessely et al., 1997), results which are different from the studies reviewed in the section above (Tiersky et al., 2003).

Reyes et al. (2003) reported on a Centers for Disease Control and Prevention (CDC) population-based prevalence study of fatigue-related disorders. The CDC used telephone calls to contact their sample of 33,997 households in Sedgewick County (Wichita) Kansas (85.7% of their sample was White). The rate of CFS was estimated to be .24%. Nisenbaum et al. (2003) reported that after their baseline survey, approximately 1,000 fatigued and 3,000 nonfatigued subjects were followed annually for 3 years. Nisenbaum et al. (2003) provided percentages of symptoms for 65 individuals classified as having CFS, and unrefreshing sleep was 95.4%, unusual fatigue postexertion was 78.5%, and difficulty thinking/concentrating or memory problems was 76.9%. Of the sample, 77% described their onset as gradual, which is in contrast to the sudden onset found in most tertiary samples. In addition, only 20–33% of the participants with CFS who were followed for up to 3 years were classified as having CFS at follow-up, while only 57% experienced partial or total remission by the end of the follow-up. A review of prospective outcome tertiary care studies in CFS patients (Cairns and Hotopf, 2005; Joyce et al., 1997) reveals that substantial recovery occurs in less than 10% of cases. It appears patients recruited from community-based samples might be very different from those from tertiary samples, at least in terms of maintenance of CFS status over time.

From 1995 to 1998, Jason and colleagues (1999f) attempted to contact a stratified sample of 28,673 households in Chicago by telephone. Of that sample, 18,675 individuals were screened for CFS symptomatology. Approximately .4% of the sample was determined to have CFS, with rates being higher among Latino and African American respondents when compared to White respondents (Jason et al., 1999f). Rates of critical CFS symptoms were 89% for memory and concentration problems, 75% for postexertional malaise, and 88% for nonrestorative sleep. Sixty-three percent reported gradual onset of symptoms. When patients with and without a premorbid psychiatric diagnosis were compared, there were no significant differences on sociodemographic variables, measures of fatigue, symptom severity, disability, stress, or coping (Jason et al., 2001c). Jason et al. (2000f) found that 65% of those diagnosed with CFS had consulted a physician regarding their fatigue, but only 9% of them had been previously diagnosed with CFS. This reveals that even of those who had been seen by a physician, very few had been appropriately diagnosed with CFS. Almost all we know about CFS comes from tertiary care samples that are primarily White and female, yet this community-based study suggests that the majority of individuals with CFS in urban areas might be people of color who have not been diagnosed and who are more functionally impaired than

Caucasians (Jason et al., 2000e). Clearly, community-based samples might be different in many ways from tertiary care samples, therefore it is important to subgroup patients on this important case ascertainment method.

Sociodemographic, Psychosocial, and Illness Subtypes

When grouping individuals diagnosed with CFS as a heterogeneous whole, it is possible that abnormalities typical of a specific subgroup are not seen, as they are obscured by the use of the entire group in the analysis. In addition, the fact that significant findings from one study are frequently not replicated is a strong indicator that each sample contains a different mix of subtypes of CFS, making replication nearly impossible.

Several investigators have suggested that patients with CFS should be subtyped on several sociodemographic variables including: gender, age, and socioeconomic status (SES). In regard to gender, CFS and chronic fatigue are more prevalent among women than men (Jason et al., 1999e,f). There is some evidence that there are gender-related differences in the impact of CFS and chronic fatigue. Among a sample of individuals with CFS, women were found to have a higher frequency of FM, tender/enlarged lymph nodes, and lower scores on the physical functioning subscale of the MOS (Medical Outcomes Study), when compared to men (Buchwald et al., 1994). In the Chicago community-based sample, gender predicted fatigue severity, with women exhibiting higher fatigue scores than men (Torres-Harding et al., 2002). Also, within this sample, women had significantly poorer physical functioning, more bodily pain, poorer emotional role functioning, significantly more severe muscle pain, and significantly greater impairment of work activities (Jason et al., 2000e). Several have suggested that findings for increased symptom severity and poorer functional outcomes among women may involve certain predisposing vulnerabilities that may be more likely to occur in women than in men (Glaser and Kiecolt-Glaser, 1998; Harlow et al., 1998; Richman and Jason, 2001).

In an influential review article, Joyce et al. (1997) concluded that older age was a risk factor for poor prognosis among individuals with CFS and chronic fatigue. For example, Clark and associates (1995) found that being over 38 years old predicted persistent illness in chronic fatigue patients. Kroenke et al. (1988) found that only a minority of patients with CFS improved and that older age was a risk factor for poorer prognosis. Tiersky et al. (2001) also found prognosis for CFS to be poor, with age being a significant predictor of outcome. Furthermore, Schmaling et al. (2003) found that older age predicted a decline in physical functioning among individuals with unexplained chronic fatigue. Finally, in the Chicago community-based sample, Jason et al. (2003c) found that those patients with CFS who were older had higher frequencies of symptoms and were more severely disabled. Conceivably, those who are older may have had more exposure to other physical illnesses or stressors, or may have suffered illness progression from CFS (Friedberg et al., 2000).

In Great Britain, Wessely et al. (1997) found higher rates of CFS for individuals of lower SES than for those of higher SES. Reeves (2003) recently reported on a national U.S. study that involved 2,728 households and found that lower income and education were the strongest predictors of fatigue. In a Chicago community-based study, Jason et al. (1999b) similarly found that individuals with lower educational and occupational status reported higher levels of fatigue than those with higher educational and occupational status. Those from the lowest SES group had significantly higher disability ratings than those from the highest SES group. Higher prevalence rates and higher fatigue levels among low income groups might be due to psychosocial and environmental risk factors. Individuals of varying socioeconomic backgrounds have been found to differ with respect to a number of issues, including health care practices (e.g., nutrition, regular exercise, routine medical examinations), behavioral risk factors (e.g., condom use, use of alcohol, drugs, and tobacco), access to adequate health care (e.g., health insurance benefits and adequacy of care provided), level of psychosocial stress (e.g., racism, discrimination, and unemployment), amount of negative environmental exposures (e.g., air pollution, lead, and other toxins), and level of hazard with respect to occupation (Davis, 1995; Perez-Stable et al., 1994; Ruiz, 1995). Some of these factors have been cited to explain observations of other medical conditions affecting low-income groups at differentially higher rates, such as HIV, hypertension, and heart disease (Friedman et al., 1999; Richardson and Piepho, 2000; Takahashi, 1997).

Findings from several investigations of CFS suggest that subtypes of patients can be distinguished with respect to mode of illness onset, whether gradual (a few hours or days) or sudden (lasting weeks or months) (DeLuca et al., 1997; Komaroff, 1988, 1994; Levine, 1997; Reyes et al., 1999). Reyes and associates (1999) found that those with sudden CFS onset reported significantly more symptoms at onset than those with gradual onset, symptoms that were more likely to be of infectious nature, including fever, sore throat, chills, and tender lymph nodes. This is consistent with other research (Komaroff, 1988, 1994), which has suggested that sudden onset of CFS may be indicative of viral/infectious illness. In a random community sample,

Jason et al. (2000f) also found that individuals with sudden CFS onset were significantly more likely to experience more severe sore throat pain. However, controversy exists as to whether prognosis of individuals with CFS is affected by the experience of sudden vs. gradual onset. Levine (1997) found that individuals with sudden onset have a better prognosis than those with gradual onset. In contrast, Reyes et al. (1999) found that over time, symptom patterns among individuals in the sample became more similar for those with sudden and gradual onset and that probability of recovery was not affected by mode of onset. Hill et al. (1999) also found that mode of illness onset was not predictive of positive or negative illness outcomes. Kennedy et al. (2004) suggested that patients be separated into precipitating factors surrounding onset because there are significant differences in clinical symptoms among those whose CFS began after military service, after exposure to organophosphate insecticides, and others who developed CFS sporadically. Another category worth considering is after exposure to an infectious disease.

Several investigators have attempted to subgroup patients on the presence vs. absence of a premorbid psychiatric condition and gradual vs. sudden onset of the illness (DeLuca et al., 1997). Johnson et al. (1999) suggested that there might be two groups of CFS patients, one with sudden onset, nonpsychiatric, and serious cognitive impairments, and the other with slow onset, psychiatric comorbidity, and mild cognitive impairment. Masuda et al. (2002a) found the noninfectious onset group to be more neurotic (the term they used), have more chronic stressors, and have more family problems than the postinfectious onset group, who were more likely to be social extroverts. Prognosis was also better for the postinfectious than the noninfectious CFS group (Masuda et al., 2002b). However, Cukor et al. (2000) did not find onset to be a predictor of psychiatric disorder, thus failing to replicate the findings of DeLuca et al. (1997). Furthermore, in a community-based sample, sudden onset of illness was associated with more, rather than less, psychiatric comorbidity (Jason et al., 2000f). These findings suggest that while onset of illness might influence the types of symptoms manifested during the beginning stages of illness, it is unclear whether onset of illness is related to prognosis.

The presence of a stressful life event preceding or precipitating onset of CFS is another factor that has been investigated and may differentiate subgroups of patients with CFS (Ray et al., 1995; Salit, 1997; Theorell et al., 1999). Some evidence indicates that individuals with CFS have experienced a higher frequency of negative life events in the time directly preceding the onset than matched controls (Salit, 1997; Theorell et al., 1999). In a community-based sample, Jason et al., and associates (2000f) found that individuals who were experiencing unusually severe stress at the time of CFS onset reported lower levels of vitality and lower emotional role functioning. Abuse histories have also been studied and these investigations broaden the types of life stressors that individuals with CFS might have encountered. For example, Taylor and Jason (2001) found that prevalence rates of sexual and physical abuse among individuals with CFS were comparable with those found in individuals with other conditions involving chronic fatigue, including those that are medically based. In addition, relative to those with CFS who report such history, most individuals with CFS did not report histories of interpersonal abuse. Other researchers (Ray et al., 1995) have found that the presence of positive life events causing moderate or major life change are associated with lower fatigue and impairment scores in individuals with CFS, while negative life events do not impact these outcomes.

Several investigators have suggested that patient subtypes can be distinguished in terms of symptom severity, functional level, and psychiatric status (Friedberg and Jason, 1998; Hickie et al., 1995; Manu et al., 1988). Hickie and associates (1995) found two distinctive subtypes: a) a "somatization-like" group, including those who have a higher prevalence of CFS symptoms and atypical symptoms, greater disability attributed to CFS and psychiatric symptoms, and a greater percentage unemployed and; b) a "CFS" group, including those individuals with lower prevalence of CFS and atypical symptoms, less disability attributed to CFS and psychiatric symptoms, and a greater percentage employed. This study has been replicated in a multisite study (Wilson et al., 2001) but there were significant intersite differences in subclass distributions. It appears that different research sites generated variability in patient groups and perhaps more attention to subtypes might help investigators to study more homogeneous groups.

Jason et al. (2003c) divided individuals with CFS into those who experienced a high and low frequency of symptoms. Those with high frequency were older, less likely to be working full-time, more likely to be unemployed, on disability, or working part-time, and more functionally disabled. But contrary to Hickie et al. (1995), psychiatric status did not vary significantly according to subtyping of individuals based on symptom frequency. Manu and associates (1988) found a bimodal distribution of symptoms among 100 chronic fatigue patients, including 21 patients with 10–15 symptoms and 79 patients with 0–9 symptoms. Hadzi-Pavlovic et al. (2000) used latent class analysis to classify patients with CFS into three classes, those with multiple severe symptoms, those with lower rates of cognitive symptoms and higher rates of pain, and

those with a less severe form of multiple symptoms (those in this latter category were younger and had a shorter duration of illness). In two follow-up studies of patients with CFS, persistent symptoms and disability at the follow-up were associated with eight or more symptoms at time one (Bombardier and Buchwald, 1995; Clark et al., 1995).

In Joyce et al.'s (1997) review article of prognostic studies, fatigue severity was one of the most consistent and important predictors of a more severe illness and poorer outcome. As an example of these studies, Laurie et al. (1997) re-surveyed a sample of individuals with CFS. This investigation found that premorbid fatigue scores were a significant predictor for developing chronic fatigue. Pheley et al. (1999) found that while recovery from CFS was rare, those patients who had less severe illness and fatigue at the initial clinic visit were more likely to have a positive prognosis. In the Chicago community-based study, Taylor et al. (2002) discovered that higher baseline fatigue scores predicted higher fatigue severity at a follow-up assessment. Those who are more fatigued experience a greater number of somatic symptoms and an increase in functional limitations. These factors might likely make it more difficult to recover from CFS and chronic fatigue. Even the construct of fatigue must be better differentiated into various dimensions (e.g., postexercise symptoms, flare-up symptoms, remission symptoms, allergy fatigue; Dechene et al., 1994). Until better differentiated subgroups are developed, it will be exceedingly difficult to identify characteristics common to all people with the diagnosis of CFS (Friedberg and Jason, 1998).

Patients diagnosed with both CFS and FM have been found to be substantially more disabled than patients with either condition alone (Bombardier and Buchwald, 1996). Jason et al. (2001c) also found that those with CFS and comorbid FM compared to those with only CFS had increased symptoms and functional impairment. Jason et al. (2000d) found in a community sample of individuals with CFS that 15.6% also had FM, 40.6% had Multiple Chemical Sensitivities (MCS), and 3.1% had FM and MCS, whereas only 40.6% had pure CFS (without FM or MCS). Future studies should subclassify patients according to whether they are pure types or have FM and/or MCS.

It is possible that CFS is experienced differently by individuals depending upon the patient's duration of illness. Recovery rates for individuals in the Reyes et al. (1999) sample were impacted by duration of illness at time of enrollment in the study, with individuals endorsing shorter duration of illness at time of enrollment being more likely to report recovery. Consistent with the findings of Reyes et al. (1999), other researchers (Clark et al., 1995; Ray et al., 1997) determined that persistent illness and poorer outcomes could be predicted by longer duration of CFS symptoms. However, Wilson and associates (1994) and Hill and associates (1999) did not find duration of illness to be a predictor of illness outcome. Discrepancies in these findings may be related to the sampling procedures employed by the researchers, selecting more severely ill individuals or those who have been ill for longer periods of time. Additionally, definitions of long vs. short duration of illness and sudden vs. gradual onset have neither been clear nor applied consistently across studies. A different approach to subtyping the illness experience would involve assessing the phase or stage of an illness (Fennell, 1995; Jason et al. 1999a, 2000a). If a researcher collapses the responses of patients in different phases, the findings might be obscured as the patients are experiencing fundamentally different processes (Jason et al., 2000b).

Medical Subgroups

The first part of this article was primarily based on self-report symptoms, and the following sections will focus on biological findings. There has been a lack of consistency in CFS laboratory findings, which may be a function of combining distinctive groups of patients into a large heterogeneous group rather than analyzing them within subtypes. In reality, there rarely is a perfect biological test for an illness, but with CFS there does appear to be mounting evidence of brain and immune system abnormalities (Komaroff, 2000a). Several researchers have suggested that there might be biomarkers that can differentiate patients with CFS into different subtypes. Below we will review some promising directions from virology, immunology, neuroendocrinology, and also from autonomic, neurologic, and genetic areas.

Virology

The onset of CFS is often linked with the recent presence of an infection. CFS has been reported as following acute mononucleosis (a viral infection), Lyme disease (a bacterial infection), and Q fever (an infection with a different type of infectious agent) (Komaroff, 2000b). For example, Lerner et al. (2002) found the presence of IgM p52 and CM_2 Human cytomegalovirus serum antibodies in 16 patients with CFS but not in another group of 18 patients with CFS. In a later study, Lerner et al. (2004) found the presence of Epstein Barr Virus VCA IgM in one group of patients with CFS but not present in other patients with CFS. These findings suggest that these serum antibodies might be diagnostic tests for subsets of patients with CFS. Lane et al. (2003) found that muscle biopsy samples from 20.8% of the CFS patients were positive for enterovirus

sequences, but all control samples were negative. Nine of the 10 enterovirus positive cases were among those with abnormal lactate response to exercise (polymerase chain reaction products were most closely related to coxsackie B virus). However, in general, when studies have looked at an association between CFS and infection, relationships have either not been found (Wallace et al., 1999) or studies have been unable to establish any one virus, such as HHV-6, as the cause of CFS (Ablashi et al., 2000).

There might be various pathways for developing CFS, with a viral infection representing just one possible route. This may be the reason that Wessely et al. (1995) found that some people with CFS had viral infections, while others had other medical illnesses, before they developed CFS. Jason et al. (2001b) did find that more patients reported an onset of CFS during January, a time when viral infections occur with the greatest frequency. In addition, it is possible that viral infection can occur in the absence of inflammation. In these cases, the virus evades the host immune system and allows the functions of the cell to continue (e.g., there is evidence of persistent cytomegalovirus infection in the pancreatic cells of people with diabetes; Wessely, 1993a,b).

It is possible that the body's reaction to one or more bacterial or viral invaders might induce symptoms in patients with CFS. Activation by macrophages due to virus or bacteria produces a release of interleukin 1, which causes an alteration in the electrical activity of the brain. It also causes a number of behavioral changes (e.g., decreases in activity and social interaction, somnolence) designed to reduce unnecessary energy expenditure, so that available energy stores can be used to fight the infection (Maier et al., 1994). For example, Sheng et al. (2001) injected an immunological stimulus that elicited a sustained upregulation of cytokines in the cerebral cortex and subcortical structures in a mouse; this coincided with marked reduction in running distance for 2 weeks. In humans, Vollmer-Conna et al. (2004) have found that the production of proinflammatory cytokines (IL-1b and IL6) were correlated with acute sickness behavior (i.e., fever, malaise, pain, fatigue, and poor concentration). Prolonged exposure to these cytokines might induce a state of chronic activation, which leads to a depletion of the stress hormone axis and to other neuroendocrine features associated with CFS (Saphier, 1994). Under these circumstances, viruses and bacteria that had previously been contained and controlled by the immune system might begin to replicate and ultimately cause symptoms for the patient.

A study by Stewart et al. (2003) compared CFS cases and controls in two different areas in upstate New York (in one of the areas, Lyndonville, a cluster of cases existed). In both areas, among those with CFS, there were elevated levels of cytotoxic T-cells. In addition, elevated levels of these T-cells were found among controls in the Lyndonville area, but not among controls in the area where a cluster of CFS cases had not occurred. These findings suggest that a common etiologic agent might have been a triggering event for an entire affected area, but that this etiologic agent might not have been sufficient to cause CFS.

Immunology

Landay et al. (1991) were the first group of researchers to find that among patients with CFS, the activation markers (CD38 and HLA-DR) had increased and the suppressor cell population (CD8 CD11b) was reduced. This research suggested that decreased suppressor cells might lead to a hyperimmune response. Several theorists have proposed that people with CFS appear to have two basic problems with immune function: a) poor cellular function, with low natural killer cell cytotoxicity and frequent immunoglobulin deficiencies (most often IgG1 and IgG3), and b) elevations of activated T lymphocytes, including cytotoxic T cells, and elevations of circulating cytokines (Evengard et al., 1999; Patarca et al., 1993; Patarca-Montero et al., 2000). Natelson et al. (2005) recently found increases in cytokines (IL-8 in some patients and IL-10 in others), and these findings support the hypothesis that in some patients with CFS, symptoms may be due to immune dysfunction within the central nervous system.

In order to better understand these findings, it is important to understand that the human body is constantly defending against bacterial, parasitic, and viral invaders (Perkel, 2001). Segerstrom and Miller (2004) have provided a useful overview of the immune system, and distinguished between natural and specific immunity. Natural immunity involve all-purpose cells that can attack a variety of pathogens. The largest group of these cells are granulocytes. These cells include neutrophils and macrophages, which are phagocytic cells that eat their targets, and the generalized response mounted by these cells is inflammation. Macrophages release communication molecules or cytokines and these can induce fever and inflammation as well as promote wound healing. Natural killer cells are also involved in natural immunity, and they are limited to early phases of viral infections (they recognize the lack of self-tissue molecules on the surface of cells and attack these cells).

Specific immunity, on the other hand, has greater specificity and takes up to several days for a full defense to be mounted. Each lymphocyte responds to only

one invader, as the receptors on their cells fit with only one molecular shape (i.e., antigen). When activated the antigen-specific cells divide to create a population of cells. There are three types of lymphocytes: T-helper cells (they produce cytokines that direct and amplify the immune response), T-cytotoxic cells (they kill cells that are infected with viruses or are otherwise compromised), and B cells (they produce proteins called antibodies that can neutralize bacterial toxins, bind to free viruses to prevent them from entering cells, or coat a toxin to increase the effectiveness of natural immunity).

In addition, the helper T cells can be separated into two classes, Th1 and Th2. Th1 cells primarily generate responses against bacteria and viruses, whereas the Th2 cells produce immune responses against extracellular parasites. Th1 operates by killing infected human cells and Th2 operates by making antibodies, which attach to normal bacteria and other pathogens outside human cells so they can be marked for killing by special cells (Van Konynenburg, 2003a). Both modes are necessary to protect against normal bacteria which stay outside the human cells, and viruses and intracellular bacteria that enter human cells. In the Th1 response, the T-helper cell produces cytokines, and they activate T-cytotoxic cells as well as natural killer cells (Segerstrom and Miller, 2004). The major proinflammatory cytokines are considered interleuken (IL-2), interferon (INF-γ), and TNF-α. The proinflammatory response clears intracellular pathogens, however if this occurs in excess it can lead to autoimmune diseases and chronic inflammation. In contrast, Th2 involves major antiinflammatory cytokines such as IL-4 and IL-10 (others include Il-5, Il-6, and Il-13), which promote humoral immunity by differentiation of B cells into antibody-secreting B cells and B cell immunoglobulin switching to IgE. These antiinflammatory cytokines inhibit production of proinflammatory cytokine and T-cell proliferation. While a highly antiinflammatory response minimizes inflammation, it can allow existing infections to linger and excessive antibody production can lead to diseases like asthma (excessive production of antibody type IgE). Those who have good health have a proper balance between pro- and antiinflammatory postures.

Several theorists have proposed that among patients with CFS, there has been a shift from Th1 to Th2 cytokines. Supporting the dominance of Th2 cytokines over the Th1 cytokines, Antoni et al. (2003) found that patients with low natural killer cell activity (NKCA) and a state of overactivation of lymphocyte subsets (e.g., CD2+CD26+ % activation markers) had the greatest fatigue intensity and greatest fatigue-related impairments in emotional and mental functioning. Hanson et al. (2001) used neural-network classifiers to also support this shift in dominance of Th2 cytokines over the Th1 cytokines. Recent research by Skowera et al. (2004) has also confirmed a Th2 bias among patients with CFS compared to controls. Subtyping patients on whether or not they have this important profile would potentially help clarify discrepant findings in the CFS literature.

Another biologically-based marker involves the 2′-5′A antiviral pathway, which causes the production of RNase-L. RNase-L is a pathway in all cells that can be activated by viral infections or toxins, with activation resulting in the destruction of messenger RNA (both that produced by the viruses and by the human cells). This is a desperate action taken by cells to prevent the proliferation of viruses, but it also interferes with the ability of cells to make its own protein. In patients with CFS, the increased levels of RNase-L occur because of a failure of the Th1 immune response to defeat intracellular infections.

Viral infections and interferon increase levels of RNase-L, which selectively degrades viral RNA. Patients with CFS have higher elevated levels of RNase-L (an 80 kDa polypeptide) than patients with any other disease, according to Suhadolnik et al. (1997), who has also found a novel low-molecular-weight (37 kDa) binding protein in a subset of individuals with CFS who are severely disabled by their disease. A European team (De Meirleir et al., 2000) has also found increased levels of 80 and 37 kDa RNase L in patients with CFS. The ratio of 37 kDa protein to the normal 80 kDa protein was high in 72% of patients with CFS, only 1% in healthy controls, and none in depression and FM control patients. Gow et al. (2001), however, did not find any evidence of upregulation of the antiviral pathway in a group with CFS and healthy controls, but did for a group of patients with infections. Even though there remains controversy on this possible biomarker, enough evidence does exist to recommend subtyping on this dimension.

Borish et al. (1998) found evidence of low level inflammation, similar to that of allergies, in a subgroup of individuals with CFS. Borish et al. suggested that there might be two subgroups of individuals with CFS, those with immune activation (infectious or inflammatory) and those devoid of immune activation with other illness processes, including psychiatric disorders. Lutgendorf et al. (1995) found that those patients with immune activation had the most severe cognitive deficits, while Natelson et al. (1993) found that those with ongoing inflammatory processes reported greater cognitive and mental disabilities. Buchwald et al. (1997) found individuals with CFS and chronic fatigue to have significant abnormalities in C-reactive protein (an indicator of acute inflammation) and neopterin (an indicator of immune system activation, malignant disease, and viral infections) when compared

to controls. Buchwald et al. stated that groups of individuals with active low-level inflammatory, infectious processes could be identified and that this was evidence of an organic process in these patients with CFS. Cook et al. (2001) found that individuals with an abnormal MRI and ongoing inflammatory processes scored significantly worse on measures of physical disability, suggesting an organic basis for some individuals with CFS. However, Brimacombe et al. (2002–03) evaluated both Gulf War Veterans and civilians with CFS and only for the Veterans found that lymphocytes were directly related to functional status (i.e., upregulation of the Th2 cytokines, Il-4 and Il-6, produced its effects on functional status via changes in cognitive abilities).

When elevated, eosinophil counts can indicate the presence of allergic inflammation, some forms of cancer, and parasitic disease. Several studies have reported significant elevations of eosinophil counts in individuals with CFS (e.g., Baraniuk et al., 1998; Conti et al., 1996). Elevated levels of lymphocytes can be indications of conditions such as viral infection, chronic infection, and Hodgkin's disease; elevated lymphocytes have also been reported for CFS samples (Patarca, 2001). An abnormal rheumatoid arthritis factor test can indicate inflammatory processes such as rheumatoid arthritis, autoimmune disease, and occasionally, infectious diseases, and the presence of rheumatoid arthritis factor has been reported in CFS samples (Kerr et al., 2001). Elevated sedimentation rates can indicate bacterial infection, pelvic inflammatory disease, systemic lupus erythematosus, and red blood abnormalities, and further, abnormal sedimentation rates have been reported in CFS samples (Richards et al., 2000). Finally, a positive ANA (antinuclear antibodies) test can indicate the presence of an inflammatory disease (systemic lupus or other rheumatoid disorders) and occasionally the presence of specific types of infections. Elevated rates of ANA have also been reported with CFS samples (Nesher et al., 2001).

Using the findings above, Corradi, Jason, and Torres-Harding (2005) recently classified individuals with CFS from the Chicago community-based epidemiology sample into three subgroups according to medical evidence of possible inflammatory processes (as evidenced by abnormal eosinophils count, antinuclear antibodies, abnormal rheumatoid arthritis factor, and abnormal sedimentation rate in the presence of an additional inflammatory marker), medical evidence of possible current infection (as evidenced by abnormal results on sedimentation rate without the presence of an inflammatory marker, or lymphocytes count), and an "other" group without evidence of either of the aforementioned organic processes (cases with more muscular, autonomic, and neurological abnormalities). Individuals from the "other" group had significantly more physical disability than those in the inflammatory group. However, those in the inflammatory group were significantly more likely to have mental difficulties (based on the mental component summary of the SF-36) and a current psychiatric diagnosis. Of interest, there were significantly more minorities than Caucasians in the infectious group. These are preliminary results but they do suggest that routine blood tests might provide useful information for subtyping patients with CFS into infectious, inflammatory, and "other" categories.

Neuroendocrinology

A variety of physical and psychological stressors can cause corticotropin-releasing hormone (CRH) to be released from the paraventricular nucleus of the hypothalamus. CRH causes adrenocorticotropin (ACTH) to be released from the anterior pituitary, and ACTH in turn, stimulates cortisol release from the adrenal cortex. A frequently cited study by Demitrack (1993) found low levels of cortisol in CFS patients, which might be due to a deficit in CRH. Deficits in cortisol have been linked to lethargy and fatigue and this deficit might be contributing to the overactive immune system.

In a summary of the literature, Scott and Dinan (1999) described patients with CFS as having a reduced adrenal secretory reserve and their adrenal glands are smaller compared to healthy subjects, whereas in major depression, enlarged adrenal glands are found. Neurotransmitters, including serotonin (5HT), are also involved in the release of CRH. Serotonin, according to Scott and Dinan, might play a role in the genesis of CFS, as altered 5HT neurotransmission seen in patients with CFS may account for disturbed sleep, muscle pain, gastrointestinal problems, and mood alterations. Scott and Dinan also mention that vasopressin (VP) also acts in a synergistic fashion with CRH in stimulating ACTH release. Low VP levels have been found in subjects with postviral fatigue syndrome. Gaab et al. (2002b) found that patients with CFS had reduced baseline ACTH levels and also found significantly lower ACTH response levels to several stress tests. However, Gaab et al. (2003) later found no CFS versus healthy control cortisol differences after administration of low-dose or high-dose ACTH, indicating that primary adrenal insufficiency is unlikely to play a significant role in the etiology of CFS. Wessely (1993a,b) states that it is simplistic to view CFS as only a deficiency in CRH.

Still, some abnormality in CRH metabolism possibly is associated with CFS. Chaudhuri and Behan (2004)

speculate that there might be different neuroendocrine processes in different individuals that ultimately lead to chronic fatigue. For example, enhanced negative feedback of the HPA axis could account for alterations in HPA functioning in patients with CFS (prolonged suppression of cortisol has been found in patients with CFS after administration of .5 mg of dexamethoasone, a steroid that causes the adrenals to stop producing cortisol) (Gaab et al., 2002a). Possibly, increased sensitivity of lymphocytes to glucocorticoids might lead to the Th2 shift (Skowera et al., 2004). Alternatively, Murphy et al. (2004) state that progesterone is a key precursor of cortisol and among patients with CFS there might be a diversion of progesterone metabolism away from cortisol pathways and toward production of ring A-reduced metabolites of progesterone (particularly isopregnanolone). There is evidence that some CFS symptoms can be caused by elevated levels of progesterone metabolites. Another possibility is that chronic cortisol deficiency can cause an overproduction of interleukin-6 (Il-6), which has been associated with symptoms of CFS (Arnold et al., 2002). It is possible that some patients with CFS have a cortisol deficiency and others do not, but when all patients are combined into one large CFS category, these important differences are ignored.

Short-term or acute stress generally has a beneficial effect on the immune system, as stress raises the output of glucocorticoids. White blood cell counts in the peripheral blood decrease as white blood cells move from the blood into tissues so that they are ready to fight infections. However, when stress occurs for weeks or months, and glucocorticoid levels are maintained at a high level for longer periods of time, the immune system is suppressed. Cohen et al. (2002) have found that individuals who show greater cortisol reactivity to acute stressors had increased risk for upper respiratory infection when naturalistic levels of stress were high. In addition to inflammation being suppressed by long-term stress, the Th1 immune response (which is critical for defending against viral, intracellular bacterial, and fungal infections) is also suppressed. The immune response is then shifted to a Th2 immune response mechanism. Stress also causes the sympathetic nervous system to activate. The sympathetic system signals the medullas of the adrenal glands to secrete adrenalin and noradrenalin, which in turn can induce a Th1 to Th2 immune response shift.

Clauw and Chrousos (1997) maintain that stress hormones suppress cellular immune function and leave intact or stimulate humoral immune function. Clauw and Chrousos summarized studies which indicate that the changes in the immune system seen in patients with CFS are common in other chronic stressful conditions such as recent widows, spouses of Alzheimer's patients, and with animals exposed to inescapable stress. Because clinically dissimilar stressors lead to the same immune changes, Clauw and Chrousos feel that hormonal changes in people with CFS are primary and immune changes secondary.

Clauw and Chrousos (1997) suggest that individuals who develop CFS might be genetically predisposed to development of the condition. Endicott (1999), for example, has found that patients with CFS have parents with increased prevalence of cancer and autoimmune disorders when compared to control patients' families. Torres-Harding, Jason, and Turkoglu (in press) found that persons with CFS were significantly more likely to report a family history of metabolic disorders when compared to a control group. Clauw and Chrousos further posit that susceptible individuals might evidence a number of organ-specific illnesses before finally progressing to develop CFS. Supportive data is also available for this thesis, as prior to developing CFS, patients have significantly more upper respiratory tract infections, lethargy, and vertigo than controls (Hamilton et al., 2001). Lyden et al. (2001) found that when healthy controls stopped exercising for a week, those that went on to develop somatic symptoms had baseline (preexercise cessation) differences in HPA axis (lower cortisol), autonomic nervous system function (more heart rate variability), and NK cell number and function (attenuated response to stress). This study suggests that lifestyle change following a stressor (e.g., trauma or infection) might contribute to CFS symptom development in some predisposed individuals. Persons with CFS might have hyperactive premorbid lifestyles and this high "action-proneness" might also be a predisposing factor for developing CFS (Van Houdenhove et al., 1995). Moreover, Clauw and Chrousos suggest that once the individual develops CFS, which can occur abruptly or slowly through viral infections or emotional stressors, there is a blunting of the human stress response. Symptom heterogeneity may be due to different axes of the stress response acting either independently or concurrently functioning in an aberrant way. This pattern might typify some patients with CFS, therefore efforts are needed to better develop ways to subgroup on this dimension, as some individuals might be in an early and others in a later phase of the illness process.

Van Konynenburg (2003b) theorizes that when a person with a certain genetic makeup is subjected to long-term stressors, the HPA axis and sympathetic nervous system become upregulated. These raise the secretion of glucocorticoids and catecholamines (adrenalin and noradrenalin), which cause a Th1 to Th2 immune response shift. Because of the shift to Th2, the body does not have an effective defense against viral or intracellular bacterial

infections. For example, the Epstein Barr virus can become active and produce infections. The immune system tries to respond but it cannot do so effectively because of the suppression of the immune system by the HPA axis and the sympathetic nervous system. Later, the HPA axis becomes downregulated but there is still not an effective Th1 response to attack the viral infection, however, now the immune system may cause inflammation (explaining elevated antinuclear antibody levels). The patient with CFS now has ineffective protection from viruses and intracellular bacteria or from inflammation. However, Cleare (2004) suggests that neuroendocrine changes occur late in the history of the illness and are in response to features of the illness such as sleep disturbance and physical deconditioning. Cleare cites two prospective studies that indicate that being fatigued during 6 months after an acute precipitant is not associated with HPA axis underactivity.

Autonomic Nervous System

The autonomic nervous system consists of the sympathetic and parasympathetic systems. The sympathetic system can cause large quantities of epinephrine (known as adrenaline) and norepinephrine to enter the bloodstream (when nerves activate the inner portion of the adrenals). Epinephrine and norepinephrine exert somewhat similar actions on the body, helping the body combat a stressor by increasing the heart rate, increasing the blood pressure by constricting blood vessels in extremities, dilating coronary arteries to get more blood flow, releasing glucose into the blood for more energy, increasing mental alertness, and slowing digestion. In contrast, the parasympathetic system calms down the body by slowing down the heart rate, reducing blood pressure, decreasing the breathing rate, and increasing the rate of digestion.

Acetylcholine is a primary neurotransmitter of the parasympathetic nervous system and is widely distributed throughout the brain and spinal cord. Chaudhuri et al. (1997) believe that CFS entails a depletion of this acetylcholine and increased sensitivity of the postsynaptic acetylcholine receptors. In Chaudhuri et al.'s (1997) research, they studied growth hormone levels in patients with CFS, healthy controls, and those with chronic exposure to organophosphate (workers who are chronically exposed to organophosphates show neurobehavioral symptoms similar to those of people with CFS). One hour after these participants were given pyridostigmine, a substance that increases the amount of acetylcholine and functions to increase the amount of growth hormone, both patient groups had a larger amount of growth factor released in comparison to healthy controls, suggesting that a similar mechanism might be at work in patients with CFS and in those with chronic organophosphate exposure. Acetylcholine hypersensitivity at the hypothalamic level is the most likely explanation of these findings.

The sympathetic system should be dominant during the day, whereas the parasympathetic system should be more active during the evening. If the sympathetic system is too active during the night, it can disturb sleep. If the sympathetic system is persistently hyperactive, it might become overworked and have more difficulty responding to stimuli. When the body is resting, the sympathetic tone of women is actually higher than that of men, potentially making women more vulnerable to developing these types of syndromes.

Individuals who are chronically stressed have a persistent lack of cortisol. Heim et al. (2000), as well as others, believe that this might also contribute to CFS. Sympathetic nervous system hyperactivity may decrease serum cortisol and may be the common denominator for low levels of DHEAS in both inflammatory and noninflammatory diseases (Kizildere et al., 2003). Elenkov et al. (2000) reviewed evidence that norepinephrine and epinephrine inhibit the production of type 1/proinflammatory cytokines, whereas they stimulate the production of type 2/antiinflammatory cytokines thereby causing a selective suppression of Th1 responses and cellular immunity and a Th2 shift toward dominance of humoral immunity.

Heart rate variability analysis, which can be obtained through a noninvasive Holter monitor, can supply data that reflects the activity of the sympathetic and parasympathetic systems. Martinez-Lavin et al. (1997) studied 19 FM patients, of whom 10 had CFS. The patients were asked to stand upright after they had been resting in a supine position and this is meant to represent a stressful challenge to the body. Controls evidenced increases in the intensity of sympathetic transmission to the heart whereas patients showed a decrease in the intensity of the sympathetic transmission to the heart, this being even more pronounced for the patients with CFS. When laying down, there was a trend among patients for an elevated heart rate, whereas when standing up, there was a drop in sympathetic output. These findings suggest that the sympathetic system might be exhausted in patients and might be incapable of responding to a stressful challenge.

There are two forms of orthostatic intolerance using the tilt table test, one characterized by a sudden drop in blood pressure, slow heart rate, and leading to fainting (neurally mediated hypotension) while the other involves increased heart rate with, or without, fainting (POTS: postural orthostatic tachycardia syndrome). A group of researchers (Bou-Holaigah et al., 1995) found that 22 of

23 patients with CFS had an abnormal response, consistent with neurally mediated hypotension. This condition occurs when the central nervous system misinterprets the body's needs when in an upright position and sends a message to the heart to slow down and lower the blood pressure, responses that are directly opposite to the responses the body needs. Van Konynenburg (2003c) summarized a talk by David Goldstein in which the heart and circulatory system's response to standing upright was explained as under the control of the sympathetic nervous system. Sympathetic nerves from the spinal cord go directly to the adrenal medulla, which produces epinephrine (adrenaline). When healthy individuals are tilted upright, their plasma norepinephrine and epinephrine levels increase about threefold, however, in patients who suffer from syncope (fainting), the norephinephrine and epinephrine both rise initially and then the epinephrine goes much higher as the norepinephrine remains at the aforementioned heightened level. This imbalance was more than tenfold; even after being restored to a supine position, the high epinephrine levels persist for hours to days and might be the reason why many patients feel so badly for days after the tilt table test. Kavelaars et al. (2000) have found among adolescent girls with CFS that baseline noradrenaline was similar in CFS and age and sex matched controls, whereas baseline adrenaline levels were significantly higher in CFS patients. Finally, Yoshiuchi et al. (2004b) used a method (i.e., ICF: instant center frequency) to more appropriately reflect shifts in sympathetic and parasympathetic activity during head-up tilt, and they separated patients with CFS into those with and without POTS, and they only found differences between those CFS patients without POTS and controls.

Other investigators have not found neurally mediated hypotension to play a major role in CFS (Poole et al., 2000). However, a recent study by Naschitz et al. (2003) did find a particular dysautonomia in CFS that differs significantly from dysautonomia in non-CFS fatigue, FM, syncope, hypertension, and healthy controls, but not in generalized anxiety disorder. In this study, the researchers computed blood pressure and heart rate changes during head-up tilt test and processed the data by image analysis methods, establishing a numerical expression as the hemodynamic instability score. These findings are particularly promising and could represent an important way of subgrouping for future research.

Another line of research has been pursued by Natelson's group, who recently found that in response to postural stress, 81% of patients with CFS and none of controls experienced ejection fraction decreases (suggesting left ventricular dysfunction in the heart), with those having more severe symptoms experiencing greater decreases (Peckerman et al., 2003a). Patients with CFS might have lower cardiac output, with the resulting low flow circulatory state possibly making it difficult for patients to meet the demands of everyday activity and leading to fatigue or other symptoms (Peckerman et al., 2003b). Peckerman et al. (2003c) suggest that deficiencies in orthostatic regulation may involve the baroreceptor reflex. In addition, Streeten and Bell (2000) found the majority of patients with CFS had striking decreases in circulating blood volume. It appears that the blood vessels in patients with CFS are constricted dramatically, but efforts to restore normal volume have met with limited success. In addition, Yoshiuchi et al. (2004a) have found that patients with CFS have lower cerebral blood flow than sedentary controls, and neither psychiatric illness nor illness severity plays a role in this reduced brain blood flow. Subtyping individuals with CFS for these types of cardiac and blood circulation problems seems warranted.

Neurology

Several investigators have found abnormalities in the cerebral white matter, which are regions of the brain that are largely or entirely composed of nerve fibers and contain few or no neuronal cell bodies or dendrites. Billiot et al. (1997) found increased microvolt levels in lower frequencies (5–7 Hz) among patients with CFS, and they suggested this could be related to cognitive problems. Earlier, a study was cited by Lange et al. (1999) that found significantly more cerebral abnormalities in a group devoid of psychiatric diagnosis than a group with CFS and a comorbid psychiatric disorder. Cook et al. (2001) compared a group of individuals diagnosed with CFS with and without brain MRI abnormalities. Individuals in the abnormal MRI group reported being more physically impaired on measures of physical disability, suggesting an organic basis to some individuals with CFS. Natelson et al. (2005) found that 30% of patients with CFS undergoing lumbar puncture had elevations of protein levels and/or in white blood cell counts relative to laboratory norms, and the group with abnormalities in the spinal fluid had a lower rate of current depression than those with normal spinal fluids. Subgrouping patients into those with normal and abnormal MRI or spinal fluid would be recommended for investigators that have access to these types of tests. Siessmeier et al. (2003) evaluated cerebral glucose metabolism (using 18-fluorodeoxyglucose positron emission tomography), and abnormalities were detectable in approximately half the CFS patients, but no specific pattern could be identified (some had hypometabolism bilaterally in the cingulate gyrus and the adjacent mesial

cortical areas, decreased metabolism in the orbitofrontal cortex, or hypometabolism in the cuneus/praecuneus). The authors conclude that PET may provide valuable information in helping to separate CFS patients into subpopulations with and without apparent alterations in the central nervous system. Using rapid event-related functional MRI, De Lange et al. (2004) found that the ventral anterior cingulate cortex was only active when healthy controls made errors on performance tasks, but not those with CFS, suggesting that CFS may be associated with dysfunctional motor planning. Using positron emission tomography (PET), Yamamoto et al. (2004) found that the density of the 5-HTT of the rostral subdivision of the anterior cingulate cortex was significantly reduced in patients with CFS, suggesting an alteration in the serotoninergic neurons in the anterior cingulate cortex might play a role in the pathophysiology of CFS. Finally, Cleare et al. (2005) found widespread reduction in 5-HT(1A) receptor binding potential, and this was particularly marked in the hippocampus bilaterally, where a 23% reduction was observed.

Zalcman et al. (1999) have found that immunogenic stimuli can alter brain circuitry, changing its sensitivity to seemingly unrelated subsequent stimuli. In addition, stress might be a conditioned stimulus that leads to an impaired immune response (Cohen et al., 1994; Gupta, 2002). Exposure to most major drugs or stress can induce long-term potentiation, such that the brain cells react more strongly (and releases dopamine more abundantly) in response to future exposures to the drug or stress (Saal et al., 2003). Gellhorn (1970) has postulated that under prolonged stimulation of the limbic-hypothalamic-pituitary axis, a lowered threshold for activation can occur. Once this system is charged, either by high-intensity stimulation or by chronically repeated low-intensity stimulation, it can sustain a high level of arousal (Gellhorn, 1968). Girdano et al. (1990) suggest that the excessive arousal can lead to an increase in the dendrites of the limbic system, which can further increase limbic stimulation. The limbic system might grow more excitatory postsynaptic receptors and decrease its inhibitory presynaptic receptors. Subsequently, people with CFS may experience excitatory neurotoxicity. Two receptors residing on the cell surface membranes of neurons are GABA (gamma aminobutyric acid), which inhibits neuronal firing and NMDA (*N*-methyl-D-aspartate), which excites neuronal firing. The GABA and NMDA receptors should be balanced, but after an injury, NMDA fires more than GABA. Minor and Hunter (2002) have proposed that prolonged exposure to inescapable stressors will eventually deplete GABA, thus reducing an important form of inhibition on excitatory glutamate transmission. Ultimately, chronic stress sensitizes neural and behavioral fear processes; this overactivation leads to fatigue (stress-induced changes can be reversed in rats by microinjections of denzodiazepines, which enhance GABA).[6] The limbic system plays a regulatory role pertaining to symptoms of fatigue, pain, memory, and cognition, and in part, it plays this role with the use of dopamine to control the NMDA receptors. These NMDA receptors might not function properly due to low levels of dopamine (Wood, 2004).

Brouwer and Packer (1994) have conducted research indicating that people with CFS might have "unstable cortical excitability associated with sustained muscle activity resulting in varied magnitudes of descending volleys" (p. 1212). Schillings et al. (2004) found reduced central activation during maximal sustained contractions of the biceps brachii muscle in patients with CFS. Davey et al. (2003) have also found that central motor mechanisms accompanying motor response preparation are impaired in patients with CFS, with this impaired function potentially leading to fluctuations in corticospinal excitability. Rather than searching for cytokine irregularities in patients with CFS, an alternative approach might involve subtyping those with and without heightened central nervous system sensitivity to stimuli such as cytokines.

Genetics

Recent twin studies of complex genetic and environmental relationships between psychological distress, fatigue, and immune system functioning, suggest that these models need to acknowledge the increasing importance of the individual's genotype (Buchwald et al., 2001; Hickie et al., 1999a). In a preliminary study, Vernon et al. (2002) used blood samples to explore gene expression profiling to distinguish five individuals with CFS from 17 controls. Eight genes were differentially expressed when comparing the CFS cases to controls and several of the expressed genes were associated with immunologic functioning (e.g., CMRF35, IL-8, HD protein), therefore implicating immune dysfunction. However, one of the CFS cases did not cluster with the other four and this could point to the occurrence of CFS subgroups. In a more recent study of 4,000 genes, 112 of those were either up or downregulated in terms of gene expression for those with CFS relative to healthy controls. Most of these gene codes for enzymes were involved in intermediary metabolism.

[6] Alternatively, Hannestad et al. (2004) found abnormal high amounts of GABA in the urine of patients with CFS. This suggests that there might be abnormally high levels of GABA in the central nervous system, and high levels of GABA could induce side-effects such as fatigue and other typical CFS-symptoms.

They also were able to separate those into rapid onset and delayed onset groups, based on gene expression (the majority of the genes upregulated in the rapid onset group were those associated with metabolism) (Van Konynenburg, 2003d).

Gow et al. (2005) reported gene expression data on eight male patients with CFS and matched controls, and concluded: a) there is a shift of immune response with preferential antigen presentation to MHC class II receptors and downregulation of the MHC class I system (with consequential suppression of the Natural Killer cells), b) increased cell membrane prostaglandin-endoperoxide synthase activity and downstream changes in oxygen transport, and c) macrophage activation with phagocytosis of apoptotic neutrophils. This research team suggests that CFS might involve ion transport and ion channel activity, and neurons use these channels to generate action potentials and release neurotransmitters at synaptic terminals. Muscle fatigue and postexertional malaise may relate to shift of membrane hyperpolarization potential (Chaudhuri et al., 2005). Sustained changes in cell membrane function may follow exposure to infections and neurotoxins as when Ciguatera toxin irreversibly inactivates sodium channels in an open mode, and these can cause delayed symptoms of chronic fatigue.

Finally, a null mutation in the globulin gene has been associated with familial corticosteroid-binding globulin deficiency and CFS (Torpy et al., 2001), and Torpy et al. (2004) has recently suggested that homozygosity for the serine allele of the corticosteroid-binding globulin gene may predispose some individuals to developing CFS. Narita et al. (2003) has found an association between long allelic variants in the serotonin transporter gene promoter and susceptibility to CFS.

Pharmacological and Alternative Treatments

Treatment ultimately will be based on a better understanding of this syndrome's etiology and pathophysiology. If there are distinct subgroups, as has been suggested in this article, then treatments might need to be tailored to the differential needs of patients with CFS. As mentioned above, one promising theory involves an imbalance between GABA and NMDA. GABA inhibits neuronal firing while NMDA excites neuronal firing. The GABA and NMDA receptors should be balanced, but after an injury or illness like CFS, NMDA might fire more than GABA. Several drugs that downregulate NMDA receptor firing (benzodiazepine therapy, magnesium, Nimotop, melatonin, calcium channel blockers) have been reported to be helpful for people with CFS (Goldstein, 1990). Natelson et al. (1996) found that low-dose treatment with a monamine oxidase inhibitor produced a significant pattern of improvement in CFS patients, thus providing support for the hypothesis that CFS might involve increased neuronal firing in the locus coeruleus.

Because hypocortisolism has been suggested as a contributing factor to CFS, several pharmacological studies have attempted to increase cortisol levels. Research by Snorrason et al. (1996) found that 70% of CFS patients reported a minimum of 30% improvement when treated with galanthamine hydrobromide, which increases plasma levels of cortisol. A study by McKenzie et al. (1998) found that a dosage of 25–35 mg resulted in only minimal therapeutic improvements while causing substantial adrenal suppression. In contrast, a study by Cleare et al. (1999), which used a lower dose (5 or 10 mg daily of hydrocortisone) led to significant reductions in self-rated fatigue and disability in patients with CFS and there was no compensatory suppression of endogenous cortisol production. More research clearly needs to be conducted in this area in order to better understand which subgroups respond optimally to which treatments. Regardless of the medication, it is important to note that very few pharmacological agents have been well-established as effective (Reid et al., 2000). What may work well for one person may not be tolerated by, or may be ineffective for, another person, reemphasizing the need to study CFS subgroups.

Nonpharmacological Interventions

Many nonpharmacological interventions have emphasized cognitive and behavioral factors in the etiology and maintenance of CFS (Vercoulen et al., 1998). However, the stereotype of patients with CFS being perfectionistic and having negative attitudes toward psychiatry has not been supported (Wood and Wessely, 1999). Clearly, exacerbation of symptoms might trigger maladaptive appraisals and coping strategies, which may further perpetuate symptomatic episodes via affective, neuroendocrine, and immunologic pathways (Antoni et al., 1994).

Turk et al. (1996) classified FM patients into one of the three profiles: Dysfunctional (DYS: high levels of pain, functional limitation, and affective distress), Interpersonally Distressed (ID: similar to DYS but further characterized by low levels of support from their significant other), and Adaptive Coper (AC: low levels of pain, distress, and disability). Turk et al. (1998) found that patients within these subgroups responded differently to a standard rehabilitation treatment protocol. Patients in the DYS group improved in most areas, whereas the ID patients failed to respond to the treatment. There was little change in

the AC patients. It would be useful to assess whether patients with CFS could be similarly subgrouped, and then assess whether these subgroups differentially respond to interventions.

Cognitive Behavior Therapy (CBT) interventions have been described as one of the more promising treatment approaches in a recent review article (Whiting et al., 2001). Results of short-term studies that have employed CBT with graded exercise suggest that this form of treatment is more effective in improving physical functioning than relaxation training (Deale et al., 1997; Sharpe et al., 1996). In the Sharpe et al. study, 63% of the subjects in the CBT condition (versus 20% of the control group) improved significantly in work status and there were significant reductions in fatigue severity as well. Similarly, in the Deale et al. clinical trial, 70% of CBT completers (versus 19% of the control group) achieved substantial improvements in physical and role functioning. However, in Deale et al.'s (2001) 5-year follow-up study, only 23% of those provided with CBT said they had completely recovered. While positive short-term results have been replicated (Powell et al., 2001), other investigators utilizing therapists with less intensive training have had positive but fewer successful outcomes (Prins et al., 2001). Van Hoof (2004) in a critique of Prins et al.'s study maintains that 28% did not complete the CBT study and that those patients with passive pattern activity did not show evidence of improvement following CBT. In addition, Van Hoff mentions that the effects of CBT were no longer present after 3 years.

While CBT has been applied to several medical problems, from pain to FM, its application to CFS has been more controversial. In part, this is due to several of the components of CBT as it is practiced by some European investigators, including the notions such as: resting is not helpful, increasing levels of exercising is critical, and patients need to be convinced that the disorder does not have a viral or medical etiology. Because the findings of the British studies have been widely disseminated, it is not uncommon for medical practitioners today to encourage patients with CFS to begin an exercise program (often without the understanding or knowledge about the need for slow, graded increases) and to challenge their beliefs about the medical etiology of their disorder. Many patient groups have been critical of these cognitive behavioral studies because they have been used to dispute either the severity or biological nature of the illness.

Typical of the purely psychogenic explanations for CFS is a research group from the Netherlands (Vercoulen et al., 1998), who believe that individuals with CFS attribute their symptoms to physical causes, are overly preoccupied by their physical limitations, and do not maintain regular activity. According to this model, these factors cause individuals with CFS to be functionally impaired, implying that the central problem with patients experiencing this condition is a psychosomatic preoccupation with one's fatigue. When Song and Jason (in press) tested this model, it fit only with the chronic fatigue participants who had psychiatric reasons for their fatigue. The fact that this model could not be replicated with either the CFS group or those with medical reasons for their chronic fatigue suggests that CFS and chronic fatigue due to psychiatric causes are not the same conditions. Data from the Netherlands' investigators who proposed this psychogenic model have provided contradictory findings. For example, when 20 ambulant patients with CFS were compared to controls, there were no differences among indices of physical fitness (Bazelmans et al., 2001), suggesting that deconditioning is not a perpetuating factor in CFS. Furthermore, van der Werf et al. (2000) found that approximately one-fourth of a sample of CFS patients differed significantly from control patients, in that they were pervasively passive. It appears that a proportion of patients with CFS have activity patterns that are comparable to those of controls, whereas only a small percentage are passively active. Werf et al. suggest that those who are most active might need to learn to moderate their activities, whereas those who are passively inactive might need to become more active. Whether or not one agrees with their recommendations, it is very likely that different patients will need very different types of interventions. As increasing or decreasing levels of activity and exercise have been a central theme in nonpharmacological interventions, it is important to understand how activity and exercise might influence physical functioning.

Scott and Dinan (1999) suggest that exercise is one of the more potent activators of the HPA axis. The theory proposes that the employment of gradual increases in activity might activate the HPA axis, which might then increase cortisol levels and alleviate some symptoms. According to the Harvard School Medical Publication *Boosting Your Energy* (2002), for healthy individuals, moderate exercise increases the body's fuel-making capacity by helping the formation of more energy-producing mitochondria in muscle cells, thereby providing cells with more energy to burn. In addition, exercise creates more capillaries and these transport oxygen to cells. Engaging in exercise can also increase the amount of time a person later spends in deep sleep, which is the type of sleep that restores energy.

Given the potential promise of interventions involving exercise, findings from patient questionnaires and some clinical trials have produced mixed results. A survey of 3,228 respondents (Preliminary report, 2001) and a separate survey sponsored by the ME Association (Cooper,

2001) found that graded exercise was felt to be the type of treatment that made more people with CFS worse than any other. Fulcher and White (1997) compared graded aerobic exercise to flexibility/relaxation training and those in the exercise group were more likely to rate themselves as improved than those in the flexibility/relaxation group (52% vs 27%). However, there was a noteworthy high dropout rate (29%) cited for this study. Wearden et al. (1998) also found high dropout rates. Edmonds et al. (2004) recently reviewed nine randomized controlled trials of using exercise, and concluded that some patients might benefit from these nonpharmacologic interventions, but that these treatments are less acceptable to patients than other approaches such as rest and pacing.

Several studies do suggest that subgroups of patients with CFS do react differently to exercise than healthy controls. For example, while in healthy controls, exercise increases pain threshold by releasing endogenous opiods and growth factors, individuals with CFS have reductions in pain threshold after modest exercise (Whiteside et al., 2004). Sorensen et al. (2003) found that patients with CFS evidenced increases in complement protein C4a at 6 hr after an exercise challenge, and symptom scores at 24 hr after exercise were significantly correlated with the C4a increase noted at 6 hr after exercise. This single protein (C4a) could be a diagnostic marker for CFS after an exercise challenge. In research reviewed earlier by Peckerman et al. (2003a), these researchers suggested that there might be left ventricular dysfunction in the heart of some patients with CFS, and lower cardiac output could make it difficult for patients to exercise. Finally, Lane et al. (2003) did find a subset of patients with CFS, who were positive for enterovirus sequences and had abnormal lactate response to exercise.

Exercising also increases the stress hormones epinephrine and norepinephrine, and in modest amounts, they can make a person feel more energized. As previously mentioned, when individuals who suffer from syncope are tilted upright, their plasma epinephrine levels escalate for hours or days, and this might be the reason why many individuals feel so badly following the table tilt test. Individuals with CFS are stress sensitive. Minimal exercise beyond what a person is accustomed to might increase levels of stress hormones and cause symptoms similar to what occurs when patients with syncope are tilted. In other words, for some individuals with low cortisol levels, activity such as exercise that increases the stress hormones epinephrine and norepinephrine, could lead to a further drop in cortisol levels. Exercise could subsequently lead to postexercise adrenal insufficiency and such a decrease could be responsible for the severe postexertional fatigue that patients with CFS experience. Boas et al. (1996) found that trained swimmers had lower resting NK-cell activity than untrained swimmers, suggesting that severe exercise might depress the immune system whereas moderate exercise might enhance the immune system. In a person with a malfunctioning HPA axis, minimal exercise might have an effect similar to that which occurs in the overtrained athlete. A recent study by Cleare (2003) found that those responders to cognitive behavior therapy (CBT; 43% of the sample at end of treatment) were the ones that had baseline urine cortisol levels of 100 (close to normal levels) whereas those who did not respond to the intervention had baseline levels of 70 (below normal levels). This indicates that those who were most impaired on HPA functioning might have been the least able to improve with graded activity interventions. Clearly, there is a need to better understand subtypes, as this might provide a clue as to why only certain patients benefit from these types of interventions.

Bruno (2004) recommends that individuals with postpolio syndrome and those with CFS not engage in exercise or activities that further stress metabolically damaged, overworked neurons. He concludes that studies recommending strengthening exercise for polio survivors actually increased muscle fatigue more than strength and did not lead to functional improvements. Too much exercise results in loss of muscle tone because muscles become weaker when poliovirus-damaged motor neurons fail. As with evidence in the CFS literature, Bruno states that deconditioning rarely occurs. However, for those who need to strengthen their hearts, he suggests a carefully monitored program incorporating paced and nonfatiguing exercise, as such can be used to strengthen and make the heart muscle work more efficiently.

Other approaches to psychotherapy, including Cognitive Coping Skills Therapy (Friedberg and Krupp, 1994), Envelope Theory (Jason et al., 1999e), pacing (Goudsmit, 1996), and pacing plus graded exercise (Wallman et al., 2004) do not challenge or question patients' beliefs in regards to the cause of CFS. For example, Envelope Theory (Jason et al., 1999e) assumes a similar perspective and does not challenge patients' beliefs of a medical cause for CFS. Instead, it recommends that patients with CFS pace their activity according to their available energy resources. In this approach, the phrase, "staying within the envelope," is used to designate a comfortable range of energy expenditure, in which an individual avoids both overexertion and underexertion, maintaining an optimal level of activity over time. The Envelope Theory would not endorse recommendations to either unilaterally increase or decrease activity. Some people with CFS need to be encouraged to increase their activity, as they have the appropriate amount of perceived

energy to do so. However, there are also people with CFS that need to be encouraged to do less in order to decrease the discrepancy between perceived and expended energy. This theory emphasizes the need to understand the differential needs of subtypes of patients with CFS. The key is to not overexpend their energy supplies or consistently go outside their "envelope" of available energy. Once this has been accomplished, it would then be possible to slowly increase the amount of activity they might engage in (King et al., 1997; Pesek et al., 2000). Rather than a cure, this approach focuses on improving the ability of patients to cope with this illness, and tailored interventions are needed for the unique needs of different subgroups of patients.

Many of these nonpharmacologic interventions deal with cognitive restructuring, coping skills, provision of psychological support, and illness education. While Miller and Cohen (2001) feel that it is still unclear whether these types of interventions influence the immune system, they have proposed an interesting theoretical model that indicates that this influence is possible. Their model begins with patients evaluating a stressful experience as a significant threat and as exceeding available coping resources, consequently eliciting negative emotional responses. They also cited studies suggesting that these negative emotional responses can cause distressed patients to engage in behaviors (e.g., altering sleep patterns, alcohol and tobacco use, decreasing physical activity) which conceivably modify immune responses. In addition, negative emotional states might activate the sympathetic division, whose fibers (descending from the brain to lymphoid tissues such as bone marrow, thymus, spleen, etc.) could release substances that influence immune responses. Distress also can activate the HPA axis and hormonal products from these systems can dysregulate the immune system. Alternatively, it is possible that motivational states or cognitive appraisals will prove to be the critical psychological mechanisms linking stress and the immune system (Segerstrom and Miller, 2004).

Long-term stress can suppress the immune system so that the host is more vulnerable to opportunistic infection and reduced control of latent herpes viruses (Miller et al., 2002). But Miller et al. (2002) additionally state that this immunosuppression does not offer an explanation for how stress might influence diseases whose primary feature is excessive inflammation. If stress suppresses the inflammatory process, then it should improve the disease course for illnesses characterized by excessive inflammation but this does not usually occur. Miller et al. provide evidence that stress alters the capacity of glucocorticoid to inhibit the production of a proinflammatory cytokine (i.e., IL-6). Segerstrom and Miller (2004) suggest that chronic stress may elicit prolonged secretion of cortisol, and white blood cells might mount a counterregulatory response by downregulating their cortisol receptors. This downregulation could reduce a cell's capacity to respond to antiinflammatory signals and as a consequence cytokine-mediated inflammatory processes might increase.

Psychological interventions might modify the way stressful circumstances are appraised and diminish the way negative emotional responses influence immune dysregulation. Relaxation, emotional-regulation training, and learning more adaptive coping responses might also decrease negative emotions. Antoni and Weiss (2003) suggest that these interventions increase a person's sense of self-efficacy and control. Further, reductions in distress can improve immunologic functioning, perhaps, in turn, reducing virally associated infections. Understanding how nonpharmacological interventions differentially affect patient subgroups might provide insights into the pathophysiology of this illness.

DISCUSSION

CFS represents a heterogeneous syndrome and the lack of consistency in related studies might very well be a function of the failure to routinely classify CFS cases into subtypes. In other words, CFS samples investigated in different studies invariably have varying critical symptoms, case ascertainment methods, degrees of psychiatric comorbidity, and sociodemographic and biologic characteristics. Currently, there is a need for investigations to develop subtypes and ultimately improve sensitivity (i.e., ability to identify those who have the subtype) and specificity (i.e., ability to correctly identify those who do not have the subtype). Even if some feel that it is premature to develop such groupings, routine collection of a standard set of variables might provide investigators with large pooled data sets to explore some of the more promising subtypes.

The current U.S. case definition for CFS (Fukuda et al., 1994) is characterized by vaguely worded criteria that lack operational definitions and guidelines to assist health care professionals in their interpretation and application of the diagnostic tool (Jason et al., 1999d). Efforts are currently underway to provide more guidelines and specific criteria for this case definition (Reeves et al., 2003). However, in spite of such efforts, some samples have included a high or low percentage of patients with critical CFS symptoms (e.g., postexertional malaise, memory and concentration problems), further complicating identification of comparable samples. The Canadian case definition does include these critical symptoms and use of such types of case definitions might aid in the selection of more homogeneous samples.

Attempts have been made to identify clinically significant methods for subgrouping. It is clear that the current cohort of individuals diagnosed with CFS is a diverse group with varying disease course and disability patterns, offering limited understanding of the etiology or pathology of the illness and its components when considered together. Patterns of illness course and duration are difficult to decipher when using the current diagnostic criteria to identify individuals with this illness. Similar to disorders such as cancer, it is highly likely that a number of distinct types of CFS exist and that the current method of grouping all individuals who meet diagnostic criteria together is complicating the identification of biological markers of the subgroups.

When diagnostic categories lack reliability and accuracy, the quality of treatment and clinical research of such populations can be significantly compromised. In other words, the validity (i.e., usefulness) of a diagnostic category is inherently limited by its reliability. Therefore, to the extent to which a diagnostic category is unreliable, a limit is placed on its validity for any clinical research or administrative use (Spitzer et al., 1975). Most importantly, if there are many distinct subtypes within a diagnostic category, samples will not be similar, as they will have different percentages of critical characteristics, symptoms, and biomarkers. For example, clinically, if a specific treatment is indicated for a given disorder, a misdiagnosis may lead to improper treatment and in cases of severe illness the matter of an incorrect diagnosis can have serious consequences. The reliability of clinical diagnosis is crucial when conducting treatment studies. If there is limited reliability of the diagnostic groups studied, because of failure to attend to subtype differences, the results of any study using such diagnostic categories are likely to be unreliable and/or invalid. Issues concerning reliability of clinical diagnosis are therefore complex and have important research and practical implications.

Cantwell (1996) purports that diagnostic criteria should specify which diagnostic instrument to use, what informants to use, and how to rate for presence and severity of the criteria. For example, one needs to specify that a certain number and type of symptoms should be present in order to make a particular diagnosis. In addition to the importance of the number and type of symptoms, future definitions of CFS should also include specific guidelines pertaining to the importance of subtypes in the diagnostic procedure. Presently, there are no such guidelines for physicians to follow when determining whether a subtype exists. Without such standardization, symptom variability will be a function of the assessment procedure and etiological factors.

If inappropriate use of a case definition leads to the inclusion of individuals who have a purely psychiatric condition, this heterogeneity of patients with CFS and psychiatric conditions will present difficulties in interpreting the results of epidemiologic and treatment studies. Inevitably, there is some risk that samples of individuals with chronic fatigue and somatic symptoms include those with solely psychiatric diagnoses, with solely CFS diagnoses, and with some CFS and psychiatric comorbidity. Therefore, these three groups need to be differentiated and analyzed separately as opposed to being collapsed into one category.

When the HPA axis and sympathetic nervous system become upregulated, possibly due to heightened central nervous system sensitivity to stimuli such as cytokines, secretions of glucocorticoids and catecholamines (adrenalin and noradrenalin) are raised. This could result in a Th1 to Th2 immune response shift, which could impair the body's defense against viral or intracellular bacterial infections. Once adrenal insufficiency stimulates immune activation, this process can contribute to brain dysfunction (Komaroff, 2000b). Further, the process might occur in different intensities and stages for different patients, thereby necessitating the need to subtype individuals on this dimension. For some individuals, cortisol levels are within normal ranges, whereas it is not for others. This might represent a critical dimension to understand the pathophysiology of this illness. Although no virus has been identified as the primary cause of CFS, the immune system seems to be fighting a virus in some patients, as evidenced by the RNase-L pathway. Evidence also points to neurological findings including hyperintense signals on MRI scans (Lange et al., 1998) and autonomic dysfunction (primarily neurally mediated hypotension; Schondorf and Freeman, 1999). In this review, we have only covered several of the subtypes that have been more extensively studied. There are other more recent subtypes, for example, the finding of chronic phase lipids in the majority of patients with CFS (Hokama et al., 2003), increased DNA fragmentation in muscle tissues of patients with FM (Sprott et al., 2004), or a deficiency in the expression of STAT1 proteins in about 30% of patients with CFS[7] (Knox et al., 2004). Many of the dimensions reviewed are worthy of efforts at subtyping in future studies. As stated by Glaser et al. (2005), inconsistent patterns of immune markers may be due to our present knowledge base in fields such as virology and immunology, and as we learn more about the immune system and new types

[7]These are a family of proteins that play central roles in the responses of cells to cytokines, which may predispose patients to developing a variety of infections.

of immune cells and cytokines are discovered, there may be other links to CFS that will help us better understand the etiology of pathophysiology of subtypes.

Finally, in our efforts to differentiate CFS subtypes, researchers have often relied on self-report measures, particularly when assessing symptoms. For example, questionnaires have become the preferred instrument in surveys assessing physical activity and fatigue (Paffenbarger et al., 1993). A practical alternative, or perhaps supplement, to the questionnaire format is use of activity logs and records. The ACTRE is an example of a daily self-administered log of physical activity (Gerber and Furst, 1992). The ACTRE provides a functional assessment of physical activity through the use of a daily log format that measures the quantity and intensity (e.g., sedentary, active, etc.) of an individual's physical activity. King et al. (2004) used this instrument and found that those with CFS, in compared to those with major depression or controls, spent significantly more time resting, significantly more time in low intensity activities (e.g., activities performed lying down), and reported significantly more time in activity that produced fatigue. Subclassifying those with and without primarily low intensity activities would represent a promising direction for future research.

However, we would recommend that self-report measures be supplemented when possible with other types of biological and physical functioning data. For example, Vanness et al. (2003) used cardiopulmonary exercise tests on patients with CFS, and patients were assigned to one of four impairment categories (i.e., none, mild, moderate, and severe). Significant differences were found between each impairment level for percentage of predicted VO_2 and peak heart rate. The authors conclude that stratifying patients by function allows for a more meaningful interpretation of the responses to exercise and may enable differential diagnosis between subsets of CFS patients.

Because cardiopulmonary exercise tests are expensive, there are other methods for assessing impairments in physical activity and functioning (Cartmel and Moon, 1992). Indirect measures of physical activity include dietary assessment and body composition measurement. Another alternative method for measuring activity involves actigraphs, which are small, light-weight, cost-efficient activity monitors that can continuously collect data every minute of the day and night for 22 days (Tryon and Williams, 1996). One important use of the actigraph is to verify self-reported improvements in physical function. Unlike most activity monitoring devices, the actigraph has the capability of recording movement intensity (Jason et al., 1999c). Using these types of monitoring devices, Ohashi et al. (2004) found patients with CFS had more abrupt interruptions of voluntary physical activity during physical activity than healthy controls, whereas Tryon et al. (2004) found that patients with CFS had a blunted circadian rhythm. Continuous actigraphy, augmented with a daily activity diary, could be incorporated into fatigue assessment and treatment in order to collect the necessary data to evaluate circadian rhythms, follow changes in it throughout treatment, and potentially subclassify patients.

The identification of clinically significant subgroups is the logical next step in furthering CFS research. Some individuals might be at higher risk of developing this chronic activation due to genetic vulnerabilities or to constitutional or psychological factors. There might be multiple pathways leading to the cause and maintenance of the neurobiologic disregulations and other symptoms experienced by individuals with CFS. Depending upon the individual and subtype, these may include unique biological, genetic, neurological, psychological, and socioenvironmental contributions. Subgrouping is the key to understanding how CFS begins, how it is maintained, how medical and psychological variables influence its course, and in the best case, how it can be prevented, treated, and cured.

ACKNOWLEDGMENTS

The authors appreciate the funding provided by NIAID (grant number AI 49720).

REFERENCES

Abbey, S. E., and Garfinkel, P. E. (1991). Neurasthenia and chronic fatigue syndrome: The role of culture in the making of a diagnosis. *Am. J. Psychiatry* **148**(12): 1638–1646.

Ablashi, D. V., Eastman, H. B., Owen, C. B., Roman, M. M., Fridman, J., Zabriskie, J. B., et al. (2000). Frequent HHV-6 reactivation in multiple sclerosis (MS) and chronic fatigue syndrome (CFS) patients. *J. Clin. Virol.* **16**(3): 179–191.

Antoni, M. H., Brickman, A., Lutgendorf, S., Klimas, N., Imia-Fins, A., Ironson, G., et al. (1994). Psychosocial correlates of illness burden in Chronic Fatigue Syndrome. *Clin. Infect. Dis.* **18** (Suppl 1): S73–S78.

Antoni, M. H., Fletcher, M. A., Weiss, D., Maher, K., Siegel, B. S., and Klimas, N. (2003, Feb.). *Impaired Natural and Heightened Lymphocyte Activation Relate to Greater Disruptions in Patients with CFS*. In: Poster presented at the Sixth International Conference on Chronic Fatigue Syndrome, Fibromyalgia, and Related Illnesses, Chantilly, VA.

Antoni, M. H., and Weiss, D. E. (2003). Stress and immunity. In Jason, L. A., Fennell, P. A., and Taylor, R. R. (eds.), *Handbook of Chronic Fatigue Syndrome*, Wiley, Hoboken, NJ, pp. 527–545.

Arnold, M. C., Papanicolaou, D. A., O'Grady, J. A., Lotsikas, A., Dale, J. K., Straus, S. E., et al. (2002). Using an interleukin-6 challenge to evaluate neuropsychological performance in chronic fatigue syndrome. *Psychol. Med.* **32**: 1075–1089.

Baraniuk, J. N., Clauw, D., Yuta, A., Ali, M., Gaumond, E., Upadhyayula, N., et al. (1998). Nasal secretion analysis in allergic rhinitis, cystic fibrosis, and nonallergic fibromyalgia/chronic fatigue syndrome subjects. *Am. J. Rhinol.* **12**: 435–440.

Barsky, A. J., and Borus, J. F. (1999) Functional somatic syndromes. *Ann. Intern. Med.* **130**: 910–921.

Bazelmans, E., Bleijenberg, G., van der Meer, J. W. M., and Folgering, H. (2001). Is physical deconditioning a perpetuating factor in chronic fatigue syndrome? A controlled study on maximal exercise performance and relations with fatigue, impairment and physical activity. *Psychol. Med.* **31**: 107–114.

Billiot, K. M., Budzynski, T. H., and Andrasik, F. (1997). EEG patterns and chronic fatigue syndrome. *J. Neurother.* **2**(2) (available at http://www.snr-jnt.org/JournalNT/JNT(2-2)4.html)

Boas, S. R., Joswiak, M. L., Nixon, P. A., Kurland, G., O'Connor, M. J., Bufalino, K., et al. (1996). Effects of anaerobic exercise on the immune system in eight-to seventeen-year-old trained and untrained boys. *J. Pediatr.* **129**: 846–855.

Bombardier, C. H., and Buchwald, D. (1995). Outcome and prognosis of patients with chronic fatigue and Chronic Fatigue Syndrome. *Arch. Intern. Med.* **155**: 2105–2110.

Bombardier, C. H., and Buchwald, D. (1996). Chronic fatigue, chronic fatigue syndrome, and fibromyalgia: Disability and health care use. *Med. Care* **34**(9): 924–930.

Boosting Your Energy. (2002). Harvard Medical School, Boston, MA.

Borish, L., Schmaling, K., DiClementi, J., Streib, J., Negri, J., and Jones, J. F. (1998). Chronic fatigue syndrome: Identification of distinct subgroups on the basis of allergy and psychologic variables. *J. Allergy Clin. Immunol.* **102**(2): 222–230.

Bou-Holaigah, I., Rowe, P. C., Kan, J., and Calkins, H. (1995). The relationship between neurally mediated hypotension and the Chronic Fatigue Syndrome. *JAMA* **274**(12): 961–967.

Brimacombe, M., Zhang, Q. W., Lange, G., and Natelson, B. H. (2002–03). Immunological variables mediate cognitive dysfunction in Gulf War Veterans but not civilians with chronic fatigue syndrome. *Neuroimmunomodulation* **10**: 93–100.

Brouwer, B., and Packer, T. (1994). Corticospinal excitability in patients diagnosed with Chronic Fatigue Syndrome. *Muscle Nerve* **17**: 1210–1212.

Bruno, R. L. (2004). *T'nts, Tips, and Techniques for Treating PPS*. (http://www.postpolioinfo.com)

Buchwald, D., Herrell, R., Ashton, S., Belcourt, M., Schmaling, K., Sullivan, P., et al. (2001). A twin study of chronic fatigue. *Psychosom. Med.* **63**: 936–943.

Buchwald, D., Pearlman, T., Kith, P., and Schmaling, K. (1994). Gender differences in patients with chronic fatigue syndrome. *J. Gen. Intern. Med.* **9**: 387–401.

Buchwald, D., Wener, M. H., Pearlman, T., and Kith, P. (1997). Markers of inflammation and immune activation in chronic fatigue and chronic fatigue syndrome. *J. Rheumatol.* **24**(2): 372–376.

Cairns, R., and Hotopf, M. (2005). A systematic review describing the prognosis of chronic fatigue syndrome. *Occup. Med.* **55**: 20–31.

Cantwell, D. P. (1996). Classification of child and adolescent psychopathology. *J. Child Psychol. Psychiatry* **37**: 3–12.

Carruthers, B. M., Jain, A. K., DeMeirleir, K. L., Peterson, D. L., Klimas, N. G., Lerner, A. M., et al. (2003). Myalgic encephalomyelitis/chronic fatigue syndrome: Clinical working case definition, diagnostic and treatments protocols. *J. Chronic Fatigue Syndr.* **11**: 7–115.

Cartmel, B., and Moon, T. (1992). Comparison of two physical activity questionnaires, with diary for assessing physical activity in an elderly population. *Clin. Epidemiol.* **45**: 877–883.

Chaudhuri, A., and Behan, P. O. (2004). Fatigue in neurological disorders. *Lancet* **363**: 978–988.

Chaudhuri, A., Behan, P. O., and Behan, W. M. H. (2005, Feb.). *Ion Channel Function and Chronic Fatigue Syndrome*. In: Paper presented at the International Conference on Fatigue Science, Karuizawa, Japan.

Chaudhuri, A., Majeed, T., Dinan, T., and Behan, P. O. (1997). Chronic Fatigue Syndrome: A disorder of central cholinergic transmission. *J. Chronic Fatigue Syndr.* **3**: 3–16.

Ciccone, D. S., Busichio, K., Vickroy, M., and Natelson, B. H. (2003). Psychiatric morbidity in the chronic fatigue syndrome. Are patients with personality disorder more physically impaired? *J. Psychosom. Res.* **54**: 445–452.

Clark, M. R., Katon, W., Russo, J., Kith, P., Sintay, M., and Buchwald, D. (1995). Chronic fatigue: Risk factors for symptom persistence in a two and one half year followup study. *Am. J. Med.* **98**: 187–195.

Clauw, D. J., and Chrousos, G. P. (1997). Chronic pain and fatigue syndromes: Overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. *Neuroimmunomodulation* **4**: 134–153.

Cleare, A. J. (2003, Feb.). *What Psychopharmacology Tells Us About the Pathophysiology of Medically Unexplained Fatigue*. In: Paper presented at the meeting towards understanding the cellular and molecular mechanisms of medically unexplained fatigue, The Brandury Center, Cold Spring Harbor Laboratory, NY.

Cleare, A. J. (2004). The HPA axis and the genesis of chronic fatigue syndrome. *Trends Endocrinol. Metab.* **15**: 55–59.

Cleare, A. J., Heap, E., Malhi, G. S., Wessely, S., O'Keane, V., and Miell, J. (1999). Low-dose hydrocortisone in chronic fatigue syndrome: A randomized crossover trial. *Lancet* **353**: 455–458.

Cleare, A. J., Messa, C., Rabiner, E. A., and Grasby, P. M. (2005). Brain 5-HT(1A) receptor binding in chronic fatigue syndrome measured using positron emission tomography and [(11)C]WAY100635. *Biol. Psychiatry* **57**: 239–246.

Cohen, N., Moynihan, J. A., and Ader, R. (1994). Pavlovian conditioning of the immune system. *Int. Arch. Allergy Immunol.* **105**: 101–106.

Cohen, S., Hamrick, N., Rodriguez, M. S., Feldman, P. J., Rabin, B. S., and Manuck, S. B. (2002). Reactivity and vulnerability to stress-associated risk for upper respiratory illness. *Psychosom. Med.* **64**: 302–310.

Conti, F., Magrini, L., Priori, R., Balesini, G., and Bonini, S. (1996). Eosinophil cationic protein serum levels and allergy in chronic fatigue syndrome. *Allergy* **51**(2): 124–127.

Cook, D. B., Lange, G., DeLuca, J., and Natelson, B. H. (2001). Relationship of brain MRI abnormalities and physical functional status in chronic fatigue syndrome. *Int. J. Neurosci.* **107**: 1–6.

Cooper, L. (2001). Report on survey of members of local ME groups. *Perspectives*.

Corradi, K. M., Jason, L. A., and Torres-Harding, S. (2005). Exploratory subgrouping in CFS: Infectious, inflammatory, and other. Manuscript submitted for publication.

Cukor, D., Tiersky, L., and Natelson, B. H. (2000). Psychiatric comorbidity and somatic distress in sudden and gradual onset chronic fatigue syndrome. *J. Chronic Fatigue Syndr.* **7**(4): 33–44.

Davey, N. J., Purf, B. K., Catley, M., Main, J., Nowicky, A. V., and Zaman, R. (2003). Deficit in motor performance correlates with changed corticospinal excitability in patients with chronic fatigue syndrome. *Int. J. Clin. Practice* **57**: 262–264.

David, A. S., Wessely, S., and Pelosi, A. J. (1991). Chronic fatigue syndrome: Signs of a new approach. *Br. J. Hosp. Med.* **45**: 158–163.

Davis, R. (1995). Racial differences in mortality: Current trends and perspectives. In: Thomas, G. E. (ed.), *Race and Ethnicity in America: Meeting the Challenge in the 21st* Century, Taylor & Francis, Washington, DC, pp. 115–126.

Deale, A., Chalder, T., Marks, I., and Wessely, S. (1997). Cognitive behaviour therapy for chronic fatigue syndrome: A randomized controlled trial. *Am. J. Psychiatry* **154**: 408–414.

Deale, A., Husain, K., Chalder, T., and Wessely, S. (2001). Long-term outcome of cognitive behavior therapy versus relaxation therapy for chronic fatigue syndrome: A 5-year follow-up study. *Am. J. Psychiatry* **158**: f2038–f2042.

Dechene, L., Friedberg, F., MacKenzie, M., and Fontanetta, R. (1994). *A New Fatigue Typology for Chronic Fatigue Syndrome*, Unpublished manuscript.

De Lange, F. P., Kalkman, J. S., Bleijenberg, G., Hagoort, P., vd Werf, S. P., van der Meer, J. W. M., et al. (2004). Neural correlates of the chronic fatigue syndrome—An fMRI study. *Brain*: 1–10 (available at http://www.cfids-cab.org/rc/de%20Lange.pdf)

DeLuca, J., Johnson, S. K., Ellis, S. P., and Natelson, B. H. (1997). Sudden versus gradual onset of chronic fatigue syndrome differentiates individuals on cognitive and psychiatric measures. *J. Psychiatr. Res.* **31**: 83–90.

DeLuca, J., and Tiersky, L. (2003). Neurocognitive assessment. In: Jason, L. A., Fennell, P., and Taylor, R. R. (eds.), *Handbook of Chronic Fatigue Syndrome*, Wiley, Hoboken, NJ, pp. 417–437.

De Meirleir, K., Bisbal, C., Campine, I., De Becker, P., Salehzada, T., Demettre, E., et al. (2000). A 37 kDa 2-5A binding protein as a potential biochemical marker for chronic fatigue syndrome. *Am. J. Med.* **108**: 99–105.

Demitrack, M. A. (1993). Neuroendocrine research strategies in chronic fatigue syndrome. In: Goodnick, P. J., and Klimas, N. G. (eds.), *Chronic Fatigue and Related Immune Deficiency Syndromes*, American Psychiatric, Washington, DC, pp. 45–66.

Dowsett, E. G., Goudsmit, E. M., Macintyre, A., and Shepherd, C. (1994). London Criteria for Myalgic Encephalomyelitis. In: Report from the National Task Force on Chronic Fatigue Syndrome (CFS), Post Viral Fatigue Syndrome (PVFS), Myalgic Encephalomyelitis (ME), Westcare, 96–98.

Dowsett, E. G., Ramsay, A. M., McCartney, R. A., and Bell, E. J. (1990). Myalgic encephalomyelitis—a persistent enteroviral infection? *Postgrad. Med. J.* **66**: 526–530.

Edmonds, M., McGuire, H., and Price, J. (2004). Exercise therapy for chronic fatigue syndrome. *Cochrane Libr.* (3): 1–22.

Elenkov, I. J., Wilder, R. L., Chrousos, G. P., and Vizi, E. S. (2000). The sympathetic nerve–An integrative interface between two supersystems: The brain and the immune system. *Pharmacol. Rev.* **52**: 595–638.

Endicott, N. A. (1999). Chronic fatigue syndrome in private practice psychiatry: Family history of physical and mental health. *J. Psychosom. Res.* **47**: 343–354.

Euba, R., Chalder, T., Deale, A., and Wessely, S. (1996). A comparision of the characteristics of Chronic Fatigue Syndrome in primary and tertiary care. *Br. J. Psychiatry* **168**: 121–126.

Evengard, B., Schacterle, R. S., and Komaroff, A. L. (1999). Chronic fatigue syndrome: New insights and old ignorance. *J. Intern. Med.* **246**: 455–469.

Fennell, P. A. (1995). The four progressive stages of the CFS experience: A coping tool for patients. *J. Chronic Fatigue Syndr.* **1**: 69–79.

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975). Mini-mental state: A practical method for grading the state of patients for the clinician. *J. Psychiatr. Res.* **12**: 189–198.

Friedberg, F., Dechene, L., McKenzie, M., and Fontanetta, R. (2000). Symptom patterns in long-term chronic fatigue syndrome. *J. Psychosom. Res.* **48**: 59–68.

Friedberg, F., and Jason, L. A. (1998). *Understanding Chronic Fatigue Syndrome: An Empirical Guide to Assessment and Treatment*, American Psychological Association, Washington, DC.

Friedberg, F., and Krupp, L. B. (1994). A comparison of cognitive behavioral treatment for chronic fatigue syndrome and primary depression. *Clin. Infect. Dis.* **18**: S105–S110.

Friedman, S. R., Chapman, T. F., Perlis, T. E., Rockwell, R., Paone, D., Sotheran, J. L., et al. (1999). Similarities and differences by race/ethnicity in changes of HIV seroprevalence and related behaviors among drug injectors in New York City, 1991–1996. *J. Acquir. Immune Defic. Syndr.* **22**: 83–91.

Fukuda, K., Straus, S. E., Hickie, I., Sharpe, M. C., Dobbins, J. G., and Komaroff, A. (1994). The Chronic Fatigue Syndrome: A comprehensive approach to its definition and study. *Ann. Intern. Med.* **121**: 953–959.

Fulcher, K. Y., and White, P. D. (1997). Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. *Br. Med. J.* **314**: 1647–1652.

Gaab, J., Huster, D., Peisen, R., Engert, V., Heitz, V., Schad, T., et al. (2002b). Hypothalamic-pituitary-adrenal axis reactivity in chronic fatigue syndrome and health under psychological, physiological, and pharmacological stimulation. *Psychosom. Med.* **64**: 951–962.

Gaab, J., Huster, D., Peisen, R., Engert, V., Heitz, V., Schad, T., et al. (2003). Assessment of cortisol response with low-dose and high-dose ACTH in patients with chronic fatigue syndrome and healthy comparison subjects. *Psychosomatics* **44**: 113–119.

Gaab, J., Huster, D., Peisen, R., Engert, V., Schad, T., Schurmeyer, T. H., et al. (2002a). Low-dose dexamethasone suppression test in chronic fatigue syndrome and health. *Psychosom. Med.* **64**: 311–318.

Gellhorn, E. (1968). CNS tuning and its implications for neuropsychiatry. *J. Nerv. Ment. Dis.* **147**: 148–162.

Gellhorn, E. (1970). The emotions and the ergotropic and trophotropic systems. *Psychol. Forsch.* **34**: 48–94.

Gerber, L. H., and Furst, G. (1992). Validation of the NIH activity record. A quantitative measure of life activities. *Arthritis Care Res.* **5**: 81–86.

Girdano, D. A., Everly, G. S., Jr., and Dusek, D. E. (1990). *Controlling Stress and Tension. A Holistic Approach*, Prentice-Hall, Englewood Cliffs, NJ.

Glaser, R., and Kiecolt-Glaser, J. K. (1998). Stress-associated immune modulation: Relevance to viral infections and chronic fatigue syndrome. *Am. J. Med.* **105**: 35–42.

Glaser, R., Padgett, D. A., Litsky, M. L., Baiocchi, R. A., Yang, E. V., Chen, M., et al. (2005). Stress-associated changes in the steady-state expression of latent Epstein-Barr virus: Implications for chronic fatigue syndrome and cancer. *Brain Behav. Immun.* **19**: 91–103.

Goldstein, J. A. (1990). *Chronic Fatigue Syndrome: The Struggle for Health*, Chronic Fatigue Syndrome Institute, Beverly Hills, CA.

Goudsmit, E. (1996). *Learning to Cope With Post-Infectious Fatigue Syndrome: A Follow-Up Study in the Psychological Aspects and Management of Chronic Fatigue Syndrome (Dissertation)*, Brunel Univeristy, Uxbridge, England.

Gow, J. W., Cannon, C., Behan, W. M. H., Herzyk, P., Keir, S., Riboldi-Tunnicliffe, G., et al. (2005, Feb). *Whole-Genome (33,000 genes) Affymetrix DNA Microassay Analysis of Gene Expression in Chronic Fatigue Syndrome*. In: Paper presented at the International Conference on Fatigue Science, Karuizawa, Japan.

Gow, J. W., Simpson, K., Behan, P. O., Chaudhuri, A., McKay, I. C., and Behan, W. M. H. (2001). Antiviral pathway activation in patients with chronic fatigue syndrome and acute infection. *Clin. Infect. Dis.* **33**: 2080–2081.

Grafman, J., Schwartz, V., Dale, J., Scheffers, M., Houser, C., and Strauss, S. (1993). Analysis of neuropsychological functioning in patients with chronic fatigue syndrome. *J. Neurol. Neurosurg. Psychiatry* **56**(6): 684–689.

Gupta, A. (2002). Unconscious amygdalar fear conditioning in a subset of chronic fatigue syndrome patients. *Med. Hypotheses* **59**: 727–735.

Hadzi-Pavlovic, D., Hickie, I. B., Wilson, A. J., Davenport, T. A., Lloyd, A. R., and Wakefield, D. (2000). Screening for prolonged fatigue syndromes: Validation of the SOFA scale. *Soc. Psychiatry Psychiatr. Epidemiol.* **35**: 471–479.

Hamilton, W. T., Hall, G. H., and Pound, A. P. (2001). Frequency of attendance in general practice and symptoms before development of chronic fatigue syndrome: A case-control study. *Br. J. Gen. Pract.* **51**: 553–558.

Hannestad, U., Theodorsson, E., and Evengard, B. (2004, Oct.). *Possible Role of Beta-Alanine and Gamma-Amino Bytyric Acid (GABA) in Chronic Fatigue Syndrome*. In: Paper presented at the International Conference on Chronic Fatigue Syndrome, Fibromyalgia, and other related illnesses, Madison, WI.

Hanson, S. J., Gause, W., and Natelson, B. (2001). Detection of immunologically signficant factors for chronic fatigue syndrome using neural-network classifiers. *Clin. Diagn. Lab. Immunol.* **8**: 658–662.

Harlow, B. L., Signorello, L. B., Hall, J. E., Dailey, C., and Komaroff, A. L. (1998). Reproductive correlates of chronic fatigue syndrome. *Am. J. Med.* **105**: 94S–99S.

Heim, C., Ehlert, U., and Hellhammer, D. H. (2000). The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. *Psychoneuroendocrinology* **25**(1): 1–35.

Hickie, I., Bennett, B., Lloyd, A., Heath, A., and Martin, N. (1999a). Complex genetic and environmental relationships between psychological distress, fatigue and immune functioning: A twin study. *Psychol. Med.* **29**: 267–277.

Hickie, I., Koschera, A., Hadzi-Pavlovic, D., Bennett, B., and Lloyd, A. (1999b) The temporal stability and co-morbidity of prolonged fatigue: A longitudinal study in primary care. *Psychol. Med.* **29**: 855–861.

Hickie, I., Lloyd, A., Wilson, A., Hadzi-Pavlovic, D., Parker, G., Bird, K., et al. (1995). Can the Chronic Fatigue Syndrome be defined by distinct clinical features? *Psychol. Med.* **25**: 925–935.

Hill, N. F. Tiersky, L. A., Scavalla, V. R., and Natelson, B. H. (1999). Fluctuation and outcome of chronic fatigue syndrome over time. *J. Chronic Fatigue Syndr.* **5**(3/4): 93–94.

Hokama, Y., Whang, C., Chun, K. F., Suma, C., Higa, N., Or, B. F. W., et al. (2003). Chronic phase lipids in sera of several chronic diseases reacting with MAB CTX (antibody to ciguatoxin). *J. Toxicol.* **22**(4): 547–554.

Holmes, G. P., Kaplan, J. E., Gantz, N. M., Komaroff, A. L., Schonberger, L. B., Strauss, S. S., et al. (1988). Chronic Fatigue Syndrome: A working case definition. *Ann. Intern. Med.* **108**: 387–389.

Hyde, B. M., Goldstein, J. A., and Levine, P. (1992). *The Clinical and Scientific Basis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome*, Nightingale Research Foundation, Ottawa, Ontario, Canada.

Jason, L. A., Fennell, P. A., Klein, S., Fricano, G., Halpert, J., and Taylor, R. R. (1999a). An investigation of the different phases of the CFS illness. *J. Chronic Fatigue Syndr.* **5**: 35–54.

Jason, L. A., Fennell, P., and Taylor, R. R. (eds.). (2003a). *Handbook of Chronic Fatigue Syndrome*, Wiley, New York.

Jason, L. A., Fennell, P. A., Taylor, R. R., Fricano, G., and Halpert, J. (2000a). An empirical verification of the Fennell phases of the CFS illness. *J. Chronic Fatigue Syndr.* **6**: 47–56.

Jason, L. A., Fricano, G., Taylor, R. R., Halpert, J., Fennell, P. A., Klein, S., et al. (2000b). Chronic fatigue syndrome: An examination of the phases. *J. Clin. Psychol.* **56**: 1497–1508.

Jason, L. A., Helgerson, J., Torres-Harding, S. R., Carrico, A. W., and Taylor, R. R. (2003b). Variability in diagnostic criteria for chronic fatigue syndrome may result in substantial differences in patterns of symptoms and disability. *Eval. Health Prof.* **26**: 3–22.

Jason, L. A., Jordan, K. M., Richman, J. A., Rademaker, A. W., Huang, C., McCready, W., et al. (1999b). A community-based study of prolonged and chronic fatigue. *J. Health Psychol.* **4**: 9–26.

Jason, L. A., King, C. P., Frankenberry, E. L., Jordan, K. M., Tryon, W. W., Rademaker, F., et al. (1999c). Chronic fatigue syndrome: Assessing symptoms and activity level. *J. Clin. Psychol.* **55**: 411–424.

Jason, L. A., King, C. P., Richman, J. A., Taylor, R. R., Torres, S. R., and Song, S. (1999d). U.S. case definition of chronic fatigue syndrome: Diagnostic and theoretical issues. *J. Chronic Fatigue Syndr.* **5**(3/4): 3–33.

Jason, L. A., King, C. P., Taylor, R. R., and Kennedy, C. (2000c). Defining chronic fatigue syndrome: Methodological challenges. *J. Chronic Fatigue Syndr.* **7**: 17–32.

Jason, L. A., Melrose, H., Lerman, A., Burroughs, V., Lewis, K., King, C. P., et al. (1999e). Managing chronic fatigue syndrome: A case study. *AAOHN J.* **47**: 17–21.

Jason, L. A., Richman, J. A., Friedberg, F., Wagner, L., Taylor, R., and Jordan, K. M. (1997). Politics, science, and the emergence of a new disease: The case of Chronic Fatigue Syndrome. *Am. Psychol.* **52**: 973–983.

Jason, L. A., Richman, J. A., Rademaker, A. W., Jordan, K. M., Plioplys, A. V., Taylor, R., et al. (1999f). A community-based study of chronic fatigue syndrome. *Arch. Intern. Med.* **159**: 2129–2137.

Jason, L. A., and Taylor, R. R. (2002). Applying cluster analysis to define a typology of chronic fatigue syndrome in a medically-evaluated, random community sample. *Psychol. Health* **17**: 323–337.

Jason, L. A., Taylor, R. R., and Carrico, A. W. (2001b). A community based study of seasonal variation in the onset of chronic fatigue syndrome and idiopathic chronic fatigue. *Chronobiol. Int.* **18**: 315–319.

Jason, L. A., Taylor, R. R., and Kennedy, C. L. (2000d). Chronic fatigue syndrome, Fibromyalgia, and Multiple Chemical Sensitivities in a community-based sample of persons with chronic fatigue syndrome-like symptoms. *Psychosom. Med.* **62**: 655–663.

Jason, L. A., Taylor, R. R., Kennedy, C. L., Jordan, K., Huang, C., Torres-Harding, S., et al. (2002a). A factor analysis of chronic fatigue symptoms in a community-based sample. *Soc. Psychiatry Psychiatr. Epidemiol.* **37**: 183–189.

Jason, L. A., Taylor, R. R., Kennedy, C. L., Jordan, K., Song, S., Johnson, D., et al. (2000e). Chronic fatigue syndrome: Sociodemographic subtypes in a community-based sample. *Eval. Health Prof.* **23**: 243–263.

Jason, L. A., Taylor, R. R., Kennedy, C. L., Jordan, K. M., Song, S., Johnson, D., et al. (2003c). Chronic fatigue syndrome: Symptom subtypes in a community based sample. *Women Health* **37**: 1–13.

Jason, L. A., Taylor, R. R., Kennedy, C. L., Song, S., Johnson, D., and Torres, S. (2000f). Chronic fatigue syndrome: Occupation, medical utilization, and subtypes in a community based sample. *J. Nerv. Ment. Dis.* **188**: 568–576.

Jason, L. A., Taylor, R. R., Kennedy, C. L., Song, S., Johnson, D., and Torres, S. (2001c). Chronic fatigue syndrome: Comorbidity with fibromyalgia and psychiatric illness. *Med. Psychiatry* **4**: 29–34.

Jason, L. A., Taylor, R. R., Plioplys, S., Stepanek, Z., and Shlaes, J. (2002b). Evaluating attributions for an illness based upon the name: Chronic fatigue syndrome, myalgic encephalopathy, and Florence Nightingale Disease. *Am. J. Community Psychol.* **30**: 133–148.

Jason, L. A., Taylor, R. R., Stepanek, Z., and Plioplys, S. (2001d). Attitudes regarding chronic fatigue syndrome: The importance of a name. *J. Health Psychol.* **6**: 61–71.

Jason, L. A., Torres-Harding, S. R., Carrico, A. W., and Taylor, R. R. (2002c). Symptom occurrence with chronic fatigue syndrome. *Biol. Psychol.* **59**: 15–27.

Jason, L. A., Torres-Harding, S. R., Jurgens, A., and Helgerson, J. (2004). Comparing the Fukuda et al. criteria and the Canadian case definition for chronic fatigue syndrome. *J. Chronic Fatigue Syndr.* **12**: 37–52.

Jason, L. A., Torres-Harding, S. R., Taylor, R. R., and Carrico, A. W. (2001e). A comparison of the 1988 and 1994 diagnostic criteria for chronic fatigue syndrome. *J. Clin. Psychol. Med. Settings* **8**: 337–343.

Johnson, S. K., DeLuca, J., and Natelson, B. (1999). Chronic fatigue syndrome: Reviewing the research findings. *Ann. Behav. Med.* **21**: 258–271.

Joyce, J., Hotopf, M., and Wessely, S. (1997). The prognosis of chronic fatigue and chronic fatigue syndrome: A systematic review. *Q. J. Med.* **90**: 223–233.

Kavelaars, A., Kuis, W., Knook, L., Sinnema, G., and Heijnen, C. J. (2000). Disturbed neuroendocrine-immune interactions in chronic fatigue syndrome. *J. Clin. Endocrinol. Metab.* **85**: 692–696.

Kennedy, G., Abbot, N. C., Spence, V., Underwood, C., and Belch, J. J. F. (2004). The specificity of the CDC-1994 criteria for chronic fatigue syndrome: Comparison of health status in three groups of patients who fulfill the criteria. *Ann. Epidemiol.* **14**: 95–100.

Kerr, J. R., Barah, F., Mattey, D. L., Laing, I., Hopkins, S. J., Hutchinson, I. V., et al. (2001). Circulating tumour necrosis factor-alpha and interferon-gamma are detectable during acute and convalescent parvovirus B19 infection and are associated with prolonged and chronic fatigue. *J. Gen. Virol.* **82**(12): 3011–3019.

King, C. P., and Jason, L. A. (2004). Improving the diagnostic criteria and procedures for chronic fatigue syndrome. *Biol. Psychol.* **68**: 87–106.

King, C. P., Jason, L. A., Frankenberry, E. L., and Jordan, K. M. (1997). Think inside the envelope. *CFIDS Chronicle, Fall*, 10–14.

King, C. P., Jason, L. A., and Pena, J. (2004). *ACTRE Variables that Differentiate Chronic Fatigue Syndrome from Depression*. Manuscript submitted for publication.

Kizildere, S., Gluck, T., Zietz, B., Scholmerich, J., and Straub, R. H. (2003). During a corticotropin-releasing hormone test in healthy subjects, administration of a beta-adrenergic antagonist induced secretion of cotisol and dehydroepiandrosterone sulfate and inhibited secretion of ACTH. *Eur. J. Endocrinol.* **148**: 45–53.

Knox, K. K., Cocchetto, A., Jordan, E., Leech, D., and Carrigan, D. R. (2004, Oct.). *Deficiency in the Expression of Stat1 Protein in a Subpopulation of Patients With Chronic Fatigue Syndrome (CFS)*. In: Paper presented at the International Conference on Chronic Fatigue Syndrome, Fibromyalgia, and other related illnesses, Madison, WI.

Komaroff, A. L. (1988). Chronic fatigue syndromes: Relationship to chronic viral infections. *J. Virol. Res.* **21**: 3–10.

Komaroff, A. L. (1994). Clinical presentation and evaluation of fatigue and chronic fatigue syndrome. In Straus, S. E. (ed.), *Chronic Fatigue Syndrome*, Marcel Dekker, New York, pp. 61–84.

Komaroff, A. L. (2000a). The biology of chronic fatigue syndrome. *Am. J. Med.* **108**: 169–171.

Komaroff, A. L. (2000b). The physical basis of CFS. *CFIDS Res. Rev.* **1**(2): 1–3, 11.

Komaroff, A. L., Fagioli, L. R., Geiger, A. M., Doolittle, T. H., Lee, J., Kornish, R. J., et al. (1996). An examination of the working case definition of Chronic Fatigue Syndrome. *Am. J. Med.* **100**: 56–64.

Kroenke, K., Wood, D., Mangelsdorff, D., Meier, N., and Powell, J. (1988). Chronic fatigue in primary care: Prevalence, patient characteristics and outcome. *JAMA* **260**: 929–934.

Landay, A. L., Jessop, C., Lennette, E. T., and Levy, J. A. (1991).Chronic fatigue syndrome: Clinical condition associated with immune activation. *Lancet* **338**: 707–712.

Lane, R. J. M., Soteriou, B. A., Zhang, H., and Archard, L. C. (2003). Enterovirus related metabolic myopathy: A postviral fatigue syndrome. *J. Neurol. Neurosurg. Psychiatry* **74**: 1382–1386.

Lange, G., DeLuca, J., Maldjian, J. A., Lee, H., Tiersky, L. A., and Natelson, B. H. (1999). Brain MRI abnormalities exist in a subset of patients with chronic fatigue syndrome. *J. Neurol. Sci.* **171**: 3–7.

Lange, G., Wang, S., DeLuca, J., and Natelson, B. H. (1998). Neuroimaging in chronic fatigue syndrome. *Am. J. Med.* **105**(SA): 50S–53S.

Lerner, A. M., Beqaj, S. H., Deeter, R. G., and Fitzgerald, J. T. (2002). IgM serum antibodies to human cytomegalovirus nonstructural gene products p52 and CM_2 (UL44 and UL57) are uniquely present in a subset of patients with chronic fatigue syndrome. *In Vivo* **16**: 153–160.

Lerner, A. M., Beqaj, S. H., Deeter, R. G., and Fitzgerald, J. T. (2004). IgM serum antibodies to Epstein-Barr virus are uniquely present in a subset of patients with chronic fatigue syndrome. *In Vivo* **18**: 101–106.

Levine, P. H. (1997). Epidemiologic advances in chronic fatigue syndrome. *J. Psychiatr. Res.* **31**(1): 7–18.

Linder, R., Dinser, R., Wagner, M., Krueger, G. R. F., and Hoffmann, A. (2002). Generation of classification criteria for chronic fatigue syndrome using an artificial neural network and traditional criteria set. *In Vivo* **16**: 37–44.

Lloyd, A. R., Hickie, I., Boughton, C. R., Spencer, O., and Wakefield, D. (1990). Prevalence of chronic fatigue syndrome in an Australian population. *Med. J. Aust.* **153**: 522–528.

Lutgendorf, S., Klimas, N. G., Antoni, M., Brickman, A., and Fletcher, M. A. (1995). Relationships of cognitive difficulties to immune measures, depression and illness burden in Chronic Fatigue Syndrome. *J. Chronic Fatigue Syndr.* **1**(2): 23–41.

Lyden, A., Ambrose, K., Petzke, F., Whalen, G., Stein, P., Chrousos, G., et al. (2001, Jan.). *Physiologic Correlates of Chronic Fatigue Syndrome-Like Symptom Development in a Subset of Healthy Individuals Deprived of Routine Aerobic Exercise*. In: Paper presented at the Annual meeting of the American Association of Chronic Fatigue Syndrome, Seattle, WA.

Maier, S. F., Watkins, L. R., and Fleshner, M. (1994). Psychoneuroimmunology. The interface between behavior, brain, and immunity. *Am. Psychol.* **49**: 1004–1017.

Manu, P., Lane, T. J., and Matthews, D. A. (1988). The frequency of the chronic fatigue syndrome in patients with symptoms of persistent fatigue. *Ann. Intern. Med.* **109**: 554–556.

Martinez-Lavin, M. Hermosillo, A. G., Mendoza, C., Ortiz, R., Cajigas, J. C., Pineda, C., et al. (1997). Orthostatic sympathetic derangement in subjects with fibromyalgia. *J. Rheumatol.* **24**(4): 714–718.

Masuda, A., Mumemoto, T., Yamanake, T., Takei, M., and Tei, C. (2002a). Psychosocial characteristics and immunological functions in patients with post infectious chronic fatigue syndrome and noninfectious chronic fatigue syndrome. *J. Behav. Med.* **25**(5): 477–485.

Masuda, A., Nakayama, T., Yamanake, T., Koga, Y., and Tei, C. (2002b). The prognosis after multidisciplinary treatment for patients with post infectious chronic fatigue syndrome and noninfectious chronic fatigue syndrome. *J. Behav. Med.* **25**(5): 487–497.

McKenzie, R., O'Fallon, A., Dale, J., Demitrack, M., Sharma, G., Deloria, M., et al. (1998). Low-dose hydrocortisone for treatment of chronic fatigue syndrome. *JAMA* **280**(12): 1061–1066.

Miller, G. E., and Cohen, S. (2001). Psychological interventions and the immune system: A meta-analytic review and critique. *Health Psychol.* **20**: 47–63.

Miller, G. E., Cohen, S., and Ritchey, A. K. (2002). Chronic psychological stress and the regulation of pre-inflammatory cytokines: A glucocorticoid-resistance model. *Health Psychol.* **21**: 531–541.

Minor, T. R., and Hunter, A. M. (2002). Stressor controllability and learned helplessness research in the United States: Sensitization and fatigue processes. *Integr. Physiol. Behav. Sci.* **37**: 44–58.

Morriss, R. K., Ahmed, M., Wearden, A. J., Mullis, R., Strickland, P., Appleby, L., et al. (1999) The role of depression in pain, psychophysiological syndromes, and medically unexplained symptoms associated with chronic fatigue syndrome. *J. Affect. Disord.* **55**: 143–148.

Moss-Morris, R., Petrie, K., Large, R., and Kydd, R. (1996). Neuropsychological deficits in chronic fatigue syndrome: Artifact or reality? *J. Neurol. Neurosurg. Psychiatry* **60**: 474–477.

Murphy, B. E., Abbott, F. V., Allison, C. M., Watts, C., and Ghadirian, A.-M. (2004). Elevated levels of some neuroative progesterone metabolites, particularly isoprenanolone, in women with chronic fatigue syndrome. *Psychoneuroendocrinology* **29**: 245–268.

Narita, M., Nishigami, N., Narita, N., Yamaguti, K., Okado, N., Watanabe, Y., et al. (2003). Association between serotonin transporter gene polymorphism and chronic fatigue syndrome. *Biochem. Biophys. Res. Commun.* **311**: 264–266.

Naschitz, J. E., Rosner, I., Rozenbaum, M., Naschitz, S., Musafia-Priselac, R., Shaviv, N., et al. (2003). The head-up tilt test with haemodynamic instability score in diagnosing chronic fatigue syndrome. *Q. J. Med.* **96**: 133–142.

Natelson, B. H., Cheu, J., Pareja, J., Ellis, S. P., Policastro, T., and Findley, T. W. (1996). Randomized, double blind, controlled placebo-phase in trial of low dose phenelzine in the chronic fatigue syndome. *Psychopharmacology* **124**: 226–230.

Natelson, B. H., Cohen, J. M., Brassloff, I., and Lee, H. J. (1993). A controlled study of brain magnetic resonance imaging in patients with fatiguing illnesses. *J. Neurol. Sci.* **120**: 213–217.

Natelson, B. H., Weaver, S. A., Tseng, C.-L., and Ottenweller, J. E. (2005). Spinal fluid abnormalities in patients with chronic fatigue syndrome. *Clin. Diagn. Lab. Immunol.* **12**: 52–55.

Nesher, G., Margalit, R., and Ashkenazi, Y. J. (2001). Anti-nuclear envelope antibodies: Clinical associations. *Semin. Arthritis Rheum.* **30**(5): 313–320.

Nisenbaum, R., Jones, J. F., Unger, E. R., Reyes, M., and Reeves, W. C. (2003). A population-based study of the clinical course of chronic fatigue syndrome. *Health Qual. Life Outcomes* **1**: 49 (Available at http://www.hqlo.com/content/1/1/49).

Nisenbaum, R., Reyes, M., Mawle, A. C., and Reeves, W. C. (1998). Factor analysis of unexplained severe fatigue and interrelated symptoms: Overlap with criteria for chronic fatigue syndrome. *Am. J. Epidemiol.* **148**: 72–77.

Nisenbaum, R., Reyes, M., Unger, E. R., and Reeves, W. C. (2004). Factor analysis of symptoms among subjects with unexplained

chronic fatigue. What can we learn about chronic fatigue syndrome? *J. Psychosom. Res.* **56**: 171–178.

Ohashi, K., Bleijenberg, G., van der Werf, S., Prins, J., Amaral, L. A. N., Natelson, B. H., et al. (2004). Decreased fractal correlation in diurnal physical activity in chronic fatigue syndrome. *Methods Inf. Med.* **43**: 26–29.

Paffenbarger, R., Blair, S., Lee, I., and Hyde, R. (1993). Measurement of physical activity to assess health effects in free living populations. *Med. Sci. Sports Exerc.* **25**: 60–70.

Patarca, R. (2001). Cytokines and chronic fatigue syndrome. *Ann. N.Y. Acad. Sci.* **933**: 185–200.

Patarca, R., Fletcher, M. A., and Klimas, N. G. (1993). Immunological correlates of chronic fatigue syndrome. In Goodnick, P. J., and Klimas, N. G. (eds.), *Chronic Fatigue and Related Immune Deficiency Syndromes*, American Psychiatric, Washington, DC, pp. 1–21.

Patarca-Montero, R., Mark, T., Fletcher, M. A., and Klimas, N. G. (2000). Immunology of chronic fatigue syndrome. *J. Chronic Fatigue Syndr.* **6**: 69–107.

Pawlikowska, T., Chalder, T., Wessely, S., Wright, D., Hirsch, S., and Wallace, P. (1994). A population based study of fatigue and psychological distress. *Br. Med. J.* **308**: 763–766.

Pazderka-Robinson, H., Morrison, J. W., and Flor-Henry, P. (2004). Electrodermal dissociation of chronic fatigue and depression: Evidence for distinct physiological mechanisms. *Int. J. Psychophysiol.* **53**: 171–182.

Peckerman, A., Chemitiganti, R., Zhao, C., Dahl, K., Natelson, B. H., Zuckler, L., et al. (2003a). Left ventricular function in chronic fatigue syndrome (CFS): Data from nuclear ventriculography studies of responses to exercise and portural stress. *FASEB* **17**(F Suppl: Part 2): A853.

Peckerman, A., LaManca, J. J., Dahl, K. A., Chemitiganti, R., Qureishi, B., and Natelson, B. H. (2003b). Abnormal impedance cardiography predicts symptom severity in chronic fatigue syndrome. *Am. J. Med. Sci.* **326**(2): 55–60.

Peckerman, A., LaManca, J. J., Qureishi, B., Dahl, K. A., Golfetti, R., Yamamoto, Y., et al. (2003c). Barorecptor reflex and integrative stress response in chronic fatigue syndrome *Psychosom. Med.* **65**: 889–895.

Perez-Stable, E. J., Marin, G., and VanOss-Marin, B. (1994). Behavioral risk factors: a comparison of Latinos and non-Latino Whites in San Francisco. *Am. J. Public Health* **84**: 971–976.

Perkel, J. M. (2001). Distinguishing Th1 and Th2 cells: Various techniques differentiate helper T cell subsets. *Scientist* **15**: 22–23.

Pesek, J. R., Jason, L. A., and Taylor, R. R. (2000). An empirical investigation of the envelope theory. *J. Hum. Behav. Soc. Environ.* **3**: 59–77.

Pheley, A. M., Melby, D., Schenck, C., Mandel, J., and Peterson, P. K. (1999). Can we predict recovery in chronic fatigue syndrome? *Minn. Med.* **82**: 52–56.

Poole, J., Herrell, R., Ashton, S., Goldberg, J., and Buchwald, D. (2000). Results of isoproterenol tilt table testing in monozygotic twins discordant for chronic fatigue syndrome. *Arch. Intern. Med.* **160**: 3461–3468.

Powell, P., Bentall, R. P., Nye, F. J., and Edwards, R. H. T. (2001). Randomized controlled trial of patient education to encourage exercise in chronic fatigue syndrome. *Br. Med. J.* **322**: 1–5.

Preliminary report (2001 Feb., 28). The severely affected. *AFME*.

Prins, J. B., Bleijenberg, G., Bazelmans, E., Elving, L. D., de Boo, T. M., Severens, J. L., et al. (2001). Cognitive behaviour therapy for chronic fatigue syndrome: A multicenter randomized controlled trial. *Lancet* **357**: 841–847.

Ramsay, M. A. (1981). *Myalgic Encephalomyelitis: A Baffling Syndrome With a Tragic Aftermath*, The ME Association.

Ramsay, M. A. (1988). *Myalgic Encephalomyelitis and Postviral Fatigue States: The Saga of Royal Free Disease*, 2nd edn., Gower, London.

Ray, C. (1991). Chronic fatigue syndrome: Conceptual and methodological ambiguities. *Psychol. Med.* **21**: 1–9.

Ray, C., Jeffries, S., and Weir, W. R. (1997). Coping and other predictors of outcome in chronic fatigue syndrome: a 1-year follow-up. *J. Psychosom. Res.* **43**(4): 405–415.

Ray, C., Jeffries, S., and Weir, W. R. C. (1995). Life-events and the course of chronic fatigue syndrome. *Br. J. Med. Psychol.* **68**: 323–331.

Regier, D. A., Boyd, J. H., Burke, J. D., Jr., Rae, D. S., Myers, J. K., Kramer, M., et al. (1988). One-month prevalence of mental disorders in the United States: Based on five Epidemiological Catchment Area sites. *Arch. Gen. Psychiatry* **45**: 977–986.

Reeves, W. C. (2003, Feb.). *Conservative Estimates of the Magnitude of Medical Unexplained Fatigue*. In: Paper presented at the meeting towards understanding the cellular and molecular mechanisms of medically unexplained fatigue, The Banbury Center, Cold Spring Harbor, NY.

Reeves, W. C., Lloyd, A., Vernon, S. D., Klimas, N., Jason, L., Bleijenberg, G., et al. (2003). Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. *BMC Health Serv. Res.* **3**: 25 (http://www.biomedcentral.com/content/pdf/1472-6963-3-25.pdf)

Reid, S., Chalder, T., Cleare, A., Hotopf, M., and Wessely, S. (2000). Extracts from "clinical evidence": Chronic fatigue syndrome. *Br. Med. J.* **320**: 292–296.

Reyes, M., Dobbins, J. G., Nisenbaum, R., Subedar, N., Randall, B., and Reeves, W. C. (1999). Chronic fatigue syndrome progression and self-defined recovery: Evidence from the CDC surveillance system. *J. Chronic Fatigue Syndr.* **5**: 17–27.

Reyes, M., Nisenbaum, R., Hoaglin, D. C., Unger, E. R., Emmons, C., Randall, B., et al. (2003) Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas. *Arch. Intern. Med.* **163**: 1530–1536.

Reynolds, K. J., Vernon, S. D., Bouchery, E., and Reeves, W. C. (2004). The economic impact of chronic fatigue syndrome. In: *Cost Effectiveness and Resource Allocation*. (available at http://resource-allocation.com/content/2/1/4).

Richards, R. S., Roberts, T. K., McGregor, N. R., Dunstan, R. H., and Butt, H. L. (2000). Blood parameters indicative of oxidative stress are associated with symptom expression in chronic fatigue syndrome. *Redox Rep. Commun. Free Radic. Res.* **5**(1): 35–41.

Richardson, A. D., and Piepho, R. W. (2000). Effect of race on hypertension and antihypertensive therapy. *Int. J. Clin. Pharmacol. Ther.* **38**: 75–59.

Richman, J. A., and Jason, L. A. (2001). Gender biases underlying the social construction of illness states: The case of chronic fatigue syndrome. *Curr. Soc.* **49**: 15–29.

Robins, L., Helzer, J., Cottler, L., and Goldring, E. (1989). *National Institute of Mental Health Diagnostic Interview Schedule* (Version Three Rev. DIS-III-R), Department of Psychiatry, Washington University School of Medicine, St. Louis, MO.

Robins, L. N., and Regier, D. A. (1991). *Psychiatric Disorders in America: The ECA Study*, Free, New York.

Ruiz, P. (1995). Assessing, diagnosing, and treating culturally diverse individuals: A Hispanic perspective. *Psychiatr. Q.* **66**: 329–341.

Saal, D., Dong, Y., Bonci, A., and Malenka, R. (2003). Drugs of abuse and stress trigger a common synaptic adaption in dopamine neurons. *Neuron* **37**(4): 577–582.

Salit, I. E. (1997). Precipitating factors for the chronic fatigue syndrome. *Journal of Psychiatr. Res.* **31**(1): 59–65.

Saphier, D. (1994, Oct). *A Role for Interferon in the Psychoneuroendocrinology of Chronic Fatigue Syndrome*. In: Paper presented at the American Association of Chronic Fatigue Syndrome Research Conference, Ft. Lauderdale, FL.

Schillings, M. L., Kalkman, J. S., van der Werf, S. P., van Engelen, B. G. M., Bleijenberg, G., and Zwarts, M. J. (2004). Diminished central activation during maximal voluntary contraction in chronic fatigue syndrome. *Clin. Neurophysiol.* **115**: 2518–2524.

Schluederberg, A., Straus, S. E., Peterson, P., Blumenthal, S., Komaroff, A. L., Spring, S. B., et al. (1992). Chronic fatigue syndrome research: Definition and medical outcome assessment. *Ann. Intern. Med.* **117**: 325–331.

Schmaling, K. B., Fiedelak, B. A., Katon, W. J., Bader, J. O., and Buchwald, D. S. (2003). Prospective study of the prognosis of unexplained chronic fatigue in a clinic-based cohort. *Psychosom. Med.* **65**: 1047–1054.

Schondorf, R., and Freeman, R. C. (1999). The importance of orthostatic intolerance in chronic fatigue syndrome. *Am. J. Med. Sci.* **317**: 117–123.

Scott, L. V., and Dinan, T. G. (1999). The neuroendocrinology of chronic fatigue syndrome: Focus on the hypothalamic-pituitary-adrenal axis. *Funct. Neurol.* **1**(14): 3–11.

Segerstrom, S. C., and Miller, G. E. (2004). Psychological stress and the human immune system: A meta-analytic study of 30 years of inquiry. *Psychol. Bull.* **130**: 601–630.

Sharpe, M., Hawton, K., Simkin, S., Surawy, C., Hackmann, A., Klimes, I., et al. (1996). Cognitive behaviour therapy for the chronic fatigue syndrome: A randomized controlled trial. *Br. Med. J.* **312**: 22–26.

Sheng, W. S., Hu, S., Ding, J. M., Chao, C. C., and Peterson, P. K. (2001). Cytokine expression in the mouse brain in response to immune activation by Corynebacterium parvum. *Clin. Diag. Lab. Immunol.* **8**(2), 446–448.

Siessmeier, T., Nix, W. A., Hardt, J., Schreckenberger, M., Egle, U. T., and Bartenstein, P. (2003). Observer independent analysis of cerebral glucose in patients with chronic fatigue syndrome. *J. Neurol. Neurosurg. Psychiatry* **74**(7): 922–928.

Skowera, A., Cleare, A., Blair, D., Bevis, L., Wessely, S. C., and Peakman, M. (2004). High levels of type 2 cytokine-producing cells in chronic fatigue syndrome. *Clin. Exp. Immunol.* **135**: 294–302.

Snorrason, E., Geirsson, A., and Stefansson, K. (1996). Trial of selective acetylcholinesterase inhibitor, galanthamine hydrobromide, in the treatment of Chronic Fatigue Syndrome. *J. Chronic Fatigue Syndr.* **2**: 35–54.

Song, S., and Jason, L. A. (in press). An effort to replicate Vercoulen et al.'s model of CFS. *Journal of Mental Health.*

Sorensen, B., Streib, J. E., Strand, M., Make, B., Gicias, P. C., Fleshner, M., et al. (2003). Complement activation in a model of chronic fatigue syndrome. *J. Allergy Clin. Immunol.* **112**: 397–403.

Spitzer, R., Endicott, J., and Robins, E. (1975). Clinical criteria for psychiatric diagnosis and DSM-III. *Am. J. Psychiatry* **132**: 1187–1192.

Spitzer, R. L., Williams, J. B. W., Gibbon, M., and First, M. B. (1995). *Structured Clinical Interview for DSM-IV - Non-Patient Edition* (SCID-NP, Version 2.0), American Psychiatric, Washington, DC.

Sprott, H., Salemi, S., Gay, R. E., Bradley, L. A., Alarcon, G. S., Oh, S. J., et al. (2004). Increased DNA fragmentation and ultrastructural changes in fibromyalgia muscle fibers. *Ann. Rheum. Dis.* **63**: 245–251.

Stewart, C. C., Cookfair, D. L., Hovey, K. M., Wende, K. E., Bell, D. S., and Warner, C. L. (2003). Predictive immunophenotypes: Disease-related profile in chronic fatigue syndrome. *Cytometry Part B (Clin. Cytometry)* **53B**: 26–33.

Streeten, D. H., and Bell, D. S. (2000). The roles of orthostatic hypotension, orthostatic tachycardia, and subnormal erythrocyte volume in the pathogenesis of the chronic fatigue syndrome. *Am. J. Med. Sci.* **320**: 1–8.

Suhadolnik, R. J., Peterson, D. L., O'Brien, K., Cheney, P. R., Herst, C. V. T., Reichenbach, N. L., et al. (1997). Biochemical evidence for a novel low molecular weight 2-5A-dependent RNase L in chronic fatigue syndrome. *J. Interferon Cytokine Res.* **7**: 377–385.

Sullivan, P. F., Smith, W., and Buchwald, D. (2002). Latent class analysis of symptoms associated with chronic fatigue syndrome and fibromyalgia. *Psychol. Med.* **32**: 881–888.

Takahashi, L. M. (1997). Stigmatization, HIV/AIDS, and communities of color: Exploring response to human service facilities. *Health Place.* **3**: 187–199.

Taylor, R. R., and Jason, L. A. (1998). Comparing the DIS with the SCID: Chronic fatigue syndrome and psychiatric comorbidity. *Psychol. Health Int. Rev. Health Psychol.* **13**: 1087–1104.

Taylor, R. R., and Jason, L. A. (2001). Sexual abuse, physical abuse, chronic fatigue, and chronic fatigue syndrome: A community-based study. *J. Nerv. Ment. Dis.* **189**: 709–715.

Taylor, R. R., Jason, L. A., and Curie, C. J. (2002). The prognosis of chronic fatigue in a community-based sample. *Psychosom. Med.* **64**: 319–327.

Taylor, R. R., Jason, L. A., and Schoeny, M. E. (2001b). Evaluating latent variable models of functional somatic distress in a community-based sample. *J. Ment. Health* **10**: 335–349.

Theorell, T., Blomkvist, V., Lindh, G., and Evengard, B. (1999). *Psychosom. Med.* **61**(3): 304–310.

Tiersky, L. A., DeLuca, J., Hill, N., Dhar, S. K., Johnson, S. K., Lange, G., et al. (2001). Longitudinal assessment of neuropsychological functioning, psychiatric status, functional disability, and employment status in chronic fatigue syndrome. *Appl. Neuropsychol.* **8**: 41–50.

Tiersky, L. A., Matheis, R. J., DeLuca, J., Lange, G., and Natelson, B. H. (2003). Functional status, neuropsychological functioning, and mood in chronic fatigue syndrome (CFS). Relationship to psychiatric disorder. *J. Nerv. Ment. Dis.* **191**: 324–331.

Torpy, D. J., Bachmann, A. W., Gartside, M., Grice, J. E., Harris, J. M., Clifton, P., et al. (2004). Association between chronic fatigue syndrome and the corticosteroid-binding globulin gene ALA SERA^{224} polymorphism. *Endocr. Res.* **30**: 417–429.

Torpy, D. J., Bachmann, A. W., Grice, J. E., Fitzgerald, S. P., Phillips, P. J., Whitworth, J. A., et al. (2001). Familial corticosteroid-binding globulin deficiency due to a novel null mutation: Association with fatigue and relative hypotension. *J. Clin. Endocrinol. Metab.* **86**: 3692–3700.

Torres-Harding, S. R., Jason, L. A., and Turkoglu, O. D. (in press). Family medical history of persons with chronic fatigue syndrome. *J. Chronic Fatigue Syndr.*

Torres-Harding, S. R., Jason, L. A., and Taylor, R. R. (2002). Fatigue severity, attributions, medical utilization, and symptoms in persons with chronic fatigue. *J. Behav. Med.* **25**(2): 99–113.

Tryon, W. W., Jason, L. A., Frankenberry, E., and Torres-Harding, S. (2004). Chronic fatigue syndrome impairs circadian rhythm of activity level. *Physiol. Behav.* **82**(5): 849–853.

Tryon, W. W., and Williams, R. (1996). Fully proportional actigraphy: A new instrument. *Behav. Res. Methods Instrum. Comput.* **28**: 392–403.

Turk, D. C., Okifuji, A., Sinclair, J. D., and Starz, T. W. (1996). Pain, disability, and physical functioning in subgroups of patients with fibromyalgia. *J. Rheumatol.* **23**: 1255–1262.

Turk, D. C., Okifuji, A., Sinclair, J. D., and Starz, T. W. (1998). Differential responses by psychosocial subgroups of fibromyalgia syndrome patients to an interdisciplinary treatment. *Arthritis Care Res.* **11**: 397–404.

Van Der Linden, G., Chalder, T., Hickie, I., Koschera, A., Sham, P., and Wessely, S. (1999) Fatigue and psychiatric disorder: different or the same? *Psychol. Med.* **29**: 863–868.

Van Hoof, E. (2004). Cognitive behavioral therapy as cure-all for CFS. *J. Chronic Fatigue Syndr.* **11**: 43–47.

Van Houdenhove, B., Onghena, P., Neerinckx, E., and Hellin, J. (1995). Does high action-proneness make people more vulnerable to Chronic Fatigue Syndrome? A controlled psychometric study. *J. Psychosom. Res.* **39**: 633–640.

Van Konynenburg, R. (2003a, July). *Comments Posted on Nancy Klimas' Presentation at the NIH CFS Workshop "Immune dysfunction observed in CFS."* Posted on co-cure@listserv.nodak.edu on July 2, 2003.

Van Konynenburg, R. (2003b, July). *Comments Posted on Esther Sternberg's Presentation at the NIH CFS Workshop "Health consequences of a dysregulated stress response."* Posted on co-cure@listserv.nodak.edu on July 1, 2003.

Van Konynenburg, R. (2003c, Oct.). *Comments Posted on David S. Goldstein's Presentation at the NIH CFS Workshop.* Posted on co-cure@listserv.nodak.edu on November 1, 2003.

Van Konynenburg, R. (2003d). *Comments Posted on Suzanne Vernon's Presentation at the NIH CFS Workshop*. Posted on co-cure@listserv.nodak.edu on June 21, 2003.

Vanness, J. M., Snell, C. R., Strayer, D. R., Dempsey, L., and Stevens, S. R. (2003). Subclassifying chronic fatigue syndrome through exercise testing. *Med. Sci. Sports Exerc*. **35**(6): 908–913.

Van Zomeren, A., and Brouwer, W. (1994). *Clinical Neuropsychology of Attention*, Oxford University Press, New York.

Vercoulen, J. H., Swanink, C. M., Galama, J. M., Fennis, J. F., Jongen, P. J., Hommes, O. R., et al. (1998). The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: Development of a model. *J. Psychosom. Res.* **45**: 507–517.

Vernon, S. D., Unger, E. R., Dimulescu, I. M., Rajeevan, M., and Reeves, W. C. (2002). Utility of the blood for gene expression profiling and biomarker discovery in chronic fatigue syndrome. *Dis. Markers* **18**: 193–199.

Vollmer-Conna, U., Fazou, C., Cameron, B., Li, H., Brennan, C., Luck, L., et al. (2004). Production of pro-inflammatory cytokines correlates with symptoms of acute sickness behaviour in humans. *Psychol. Med.* **34**: 1–9.

Wallace, H. L., 2nd, Natelson, B., Gause, W., and Hay, J. (1999). Human herpesviruses in chronic fatigue syndrome. *Clin. Diagn. Lab. Immunol.* **6**(2): 216–223.

Wallman, K. E., Morton, A. R., Goodman, C., Grove, R., and Guilfoyle, A. M. (2004). Randomised controlled trial of graded exercise in chronic fatigue syndrome. *Med. J. Aust.* **180**: 444–448.

Wearden, A., and Appleby, L. (1997). Cognitive performance and complaints of cognitive impairment in chronic fatigue syndrome. *Psychol. Med.* **27**: 81–90.

Wearden, A. J., Morriss, R. K., Mullis, R., Strickland, P. L., Pearson, D. J., Appleby, L., et al. (1998). Randomized, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome. *Br. J. Psychiatry* **172**: 485–490.

van der Werf, S., Prins, J., Vercoulen, J., van der Meer, J., and Bleijenberg, G. (2000). Identifying physical activity patterns in chronic fatigue syndrome using actigraphic assessment. *J. Psychosom. Res.* **49**: 373–379.

Wessely, S. (1993a). The neuropsychiatry of chronic fatigue syndrome. *Chronic Fatigue Syndr.* **173**: 212–237.

Wessely, S. (1993b). The neuropsychiatry of chronic fatigue syndrome. In Bock, B. R., and Whelan, J. (eds.), *Chronic Fatigue Syndrome*, Wiley, New York, pp. 212–229.

Wessely, S., Chalder, T., Hirsch, S., Pawlikowska, T., Wallace, P., and Wright, D. J. M. (1995). Postinfectious fatigue: Prospective cohort study in primary care. *Lancet* **345**: 1333–1338.

Wessely, S., Chalder, T., Hirsch, S., Wallace, P., and Wright, D. (1996). Psychological symptoms, somatic symptoms, and psychiatric disorder in chronic fatigue and chronic fatigue syndrome: A prospective study in the primary care setting. *Am. J. Psychiatry* **153**: 1050–1059.

Wessely, S., Chalder, T., Hirsch, S., Wallace, P., and Wright, D. (1997). The prevalence and morbidity of chronic fatigue and chronic fatigue syndrome: A prospective primary care study. *Am. J. Public Health* **87**: 1449–1455.

Whiteside, A., Hansen, S., and Chaudhuri, A. (2004). Exercise lowers pain threshold in chronic fatigue syndrome. *Pain* **109**: 497–499.

Whiting, P., Bagnall, A.-M., Sowden, A. J., Cornell, J. E., Mulrow, C. D., and Ramirez, G. (2001). Interventions for the treatment and management of chronic fatigue syndrome, *JAMA* **286**: 1360–1368.

Wilson, A., Hickie, I., Hadzi-Pavlovic, D., Wakefield, D., Parker, G., Straus, S. E., et al. (2001). What is chronic fatigue syndrome: Heterogeneity within an international multicentre study. *Aust. N.Z. J. Psychiatry* **35**: 520–527.

Wilson, A., Hickie, I., Lloyd, A., Hadzi-Pavlovic, D., Boughton, C., Dwyer, J., et al. (1994). Longitudinal study of outcome of chronic fatigue syndrome. *Br. Med. J.* **308**: 756–759.

Wood, B., and Wessely, S. (1999). Personality and social attitudes in chronic fatigue syndrome. *J. Psychosom. Res.* **47**: 385–397.

Wood, G., Bentall, R., Gopfert, M., Dewey, M., and Edwards, R. (1994). The differential response of chronic fatigue neurotic and muscular dystrophy patients to experimental psychological stress. *Psychol. Med.* **24**: 357–364.

Wood, P. B. (2004). Stress and dopamine: implications for the pathophysiology of chronic widespread pain. *Med. Hypotheses* **62**(3): 420–424.

Yamamoto, S., Ouchi, Y., Onoe, H., Yoshikawa, E., Tsukada, H., Takahashi, H., et al. (2004). Reduction of serotonin transporters of patients with chronic fatigue syndrome. *Brain Imaging* **15**: 2571–2574.

Yoshiuchi, K., Farkas, J., and Natelson, B. H. (2004a, May). *Patients With Chronic Fatigue Syndrome Have Reduced Cerebral Blood Flow*. In: Paper presented at the International Conference on Chronic Fatigue Syndrome, Fibromyalgia, and other related illnesses, Madison, WI.

Yoshiuchi, K., Quigley, K. S., Ohashi, K., Yamamoto, Y., and Natelson, B. H. (2004b). Use of time-frequency analysis to investigate temporal patterns of cardiac autonomic response during head-up tilt in chronic fatigue syndrome. *Auton. Neurosci.* **113**: 55–62.

Zalcman, S., Savina, I., and Wise, R. A. (1999). Interleukin-6 increases sensitivity to the locomotor-stimulating effects of amphetamine in rats. *Brain Res.* **847**: 276–283.