Chronic Fatigue Syndrome

State of the Science Conference

Presented by

The U.S. Department of Health and Human Services
Chronic Fatigue Syndrome Coordinating Committee

October 23-24, 2000
Arlington, Virginia

Overview

Chronic Fatigue Syndrome (CFS) is a debilitating and complex disorder characterized by profound fatigue that is not improved by bed rest and that may be worsened by physical or mental activity. Persons with CFS must often function at substantially lower levels of activity than they were capable of before the onset of illness. In addition to these key defining characteristics, patients report various nonspecific symptoms, including weakness, muscle pain, impaired memory and/or mental concentration, insomnia, and post-exertional fatigue lasting more than 24 hours. In some cases, CFS can persist for years. The cause or causes of CFS have not been identified, and no specific diagnostic tests are available. Moreover, since many illnesses have incapacitating fatigue as a symptom, care must be taken to exclude other known and often treatable conditions before a diagnosis of CFS is made.

The state-of-the-science conference was organized by the U.S. Department of Health and Human Services (DHHS) Chronic Fatigue Syndrome Coordinating Committee (CFSCC), with the financial assistance of several DHHS agencies (listed in Appendix 1). The goals of the meeting were to focus on CFS research areas in which information is both mature and exciting; summarize current knowledge and identify important gaps in knowledge; garner the perspective of expert investigators not currently working on the problem of CFS; and identify expert investigators who might be attracted to study CFS as a clinical problem.

Seven topic areas of medical research were identified: neuroendocrinology; cognition; chronic pain; sleep; immunology; orthostatic intolerance/neurally mediated hypotension; and fatigue, functional status, and disability. For each topic, a clinical scientist studying CFS (CFS expert) was asked to present the most provocative aspects of current knowledge; then scientists working in that same research area, but not studying CFS (subject experts), were asked to provide additional information and insights from that discipline that could enhance understanding of CFS. Each session provided time for discussion among the presenters and comments/questions from the conference attendees. A lay audience session was also included as part of the agenda. The summary of the meeting is organized around the seven scientific topic areas. The sessions have been summarized without attributing comments to individual speakers; however, the speakers provided the main content of the sessions. (Speakers are listed in Appendix 2).

Introduction

Presentations about CFS from the perspective of the patient and the community physician laid the groundwork for the scientific presentations. A CFS patient described her 11 years of living with CFS, and how her previous highly active professional and personal life style had been restricted and diminished by the illness. She has had to change jobs to accommodate her body and her symptoms. Her relationships with her physicians have varied from supportive to suspicious to suggestions that other patients may be in more need of medical assistance. She would like to be able to have the quality of life of her earlier pre-CFS years and for her and her physician to have tools to manage the illness. She noted that CFS does not exist in a vacuum, and may be one of a group of chronic diseases with similar and overlapping symptoms.

A community physician noted the problems of treating CFS in the current medical climate, which emphasizes a scientific/mechanistic basis for medical prevention, diagnosis, and

treatment. In the case of CFS, there is no known underlying disease mechanism around which to design treatment. Clearly, symptom relief is within the purview of all physicians, even without an etiology or cure for CFS. However, there is concern among some physicians that off-label use of medications or use of narcotics to treat CFS symptoms could cause problems with licensing bodies. There is also a concern by some members of the medical profession that making a CFS diagnosis or treating CFS may perpetuate illness. There is no medical specialty or sub-specialty that is identified with CFS, thus making patient referrals in the managed care environment difficult. Given that primary care physicians commonly provide much of the care for chronic illnesses with unknown etiologies, such as multiple sclerosis (MS) and rheumatoid arthritis (RA), it was suggested that these illnesses might be designated as the specialty of choice for CFS. While the research case definition of CFS is helpful for clinical studies, primary care physicians would benefit from a clinical case definition of CFS.

Many primary care physicians can "recognize" the CFS symptom constellation when they see individual patients. Disability determination is also a problem for primary care physicians. Disability claims often focus on objective tests, which are not available for CFS. Children with CFS are often denied appropriate support (e.g., tutoring), as local schools do not recognize CFS as an entity and therefore abjure responsibility for needed services.

A misperception that causes great problems is that CFS is considered by some to represent a character flaw in the patient. More education of primary care physicians about the nature of CFS and its legitimacy as an illness, the various kinds of coping styles and aggressive symptomatic treatment, and the need for patient respect and reassurance would greatly benefit the CFS patient community. More research needs to be done on CFS pathogenic mechanisms, so that physicians can prescribe treatments with confidence to patients and so that patients will be confident about the care they are receiving.

Neuroendocrinology

The neuroendocrine system is involved in the body's reaction to stress. It involves the central nervous system, endocrine glands, and a number of hormones and other mediators (including cytokines) that act in a variety of regulatory pathways and feedback loops. The stress system is designed for survival of the individual when faced with danger. It induces a state of arousal, alertness, vigilance, and cognition; and shuts down vegetative body functions, such as eating and sleeping, as well as the neuroendocrine programs involved in growth and reproduction. The regulatory pathways built into the neuroendocrine system are designed to stop the system when the danger is no longer present. It is important to recognize that the stress, immune, and sleep systems are linked to one another by several common and multifunctional mediators.

Investigations of the stress system dysregulation/disorders that are associated with changes in arousal, mood, and energy levels were undertaken initially to understand the differences between two forms of depression—atypical depression and melancholic depression—with later studies including CFS and fibromyalgia (FMS). Atypical depression is characterized by increased sleep and appetite, weight gain, and profound lethargy and fatigue. Affected persons feel out of touch with themselves. By contrast, melancholic depression is characterized by a state of hyperarousal, with anxiety, decreased concentration, and a reduction in sleeping and eating. Persons with melancholic depression feel worthless and have a sense of hopelessness about the future.

To investigate the basis for the differences in symptoms, studies focused on a corticotropin-releasing hormone (CRH), which is a neurohormone produced in the hypothalamus region of the brain and is a component of that portion of the body's stress system called the hypothalamic pituitary adrenal axis (HPA). Animal studies have shown CRH to recapitulate many of the physiological and behavioral aspects of the stress system. Studies of CRH levels have demonstrated that the hormone is down regulated in CFS, in atypical depression, and in seasonal affective disorder (SAD), but not in melancholic depression. When CFS patients are stimulated with a cortisol inducer, they have an exaggerated response to small doses and a reduced response to high doses. In both FMS and CFS, there are reduced levels of another stress mediator, norepinephrine. In addition, CRH response to exercise is blunted in CFS patients. Lower levels of CRH and HPA axis activity tend to result in hypoarousal, lethargy, decreased plasma volume, and inflammatory symptoms.

Another aspect of the body's response to stress is the shift in the type of the immune response, from cell-mediated immunity to humoral immunity. Studies in strains of rats that differ in their immune responses have shown the effect of this shift. Lewis rats, which have an enhanced immune response to multiple stimuli and thus are at risk of autoimmune diseases, have reduced levels of CRH after stress. By contrast, Fisher rats that have relatively low or suppressed immune responses responded adversely to stress, with some animals dying from a particular stressor. Thus, the immune system as a whole, as well as variations within individuals, can affect the stress response. Additional studies are needed to better understand the role of the HPA axis/stress response in CFS. Such studies would involve direct comparisons of basal levels and challenge responses of HPA axis in persons with CFS, SAD, and atypical depression.

In addition to its role in stress, CRH is a modulator of wakefulness. In animal studies, if CRH is increased, then wakefulness increases; if CRH is reduced, wakefulness decreases. In addition, interleukin-1 (IL-1), a cytokine, enhances sleep in animal models and its concentration peaks in humans at sleep onset. Studies in animal models demonstrate a balance and regulation of CRH and IL-1 by one another. They also demonstrate genetic differences between rat strains in their CRH responsiveness to IL-1. Thus, the immune and stress systems are linked by mediators not only to one another but also to sleep regulation.

Although cytokines were named for their immunomodulatory effects, they can penetrate the blood brain barrier, act as neuromodulators, and produce both acute and long-term effects in the brain, particularly in regions associated with cognition and endocrine activity. Two important aspects of this type of alteration are related to the action of cytokines in concert with other factors such as environmental stressors. Thus, IL-2 alone has only a modest effect in stimulating corticosterone in mice. However, in the presence of a relatively mild stressor (i.e. novelty stress), IL-2 results in an increased magnitude and duration of the corticosterone response. Changes in neurochemical activity as measured by dopamine levels in the nucleus accumbens (an area of the brain important for motivation) are higher during a secondary immune response than during a primary response. In addition, animals initially receiving multiple injections of IL-2 to replicate the effects of a chronic disorder showed an increased behavioral response to a highly selective dopamine uptake inhibitor 6 weeks after the initial multiple doses. There are studies in humans that also suggest that long-term alterations of the HPA axis can occur in a variety of trauma, stress, and abuse situations.

Another important concept about cytokines is that they are potent modulators of neurotransmission, and that they may induce biphasic effects on neuronal excitability (e.g., IL-2

is a very potent modulator of the NMDA (glutamate) receptor in the ventral tegmental area, a brain region associated with aspects of reward, cognition, and motor activity. Low doses of IL-2 result in inhibition of NMDA-activated current in this brain region, whereas high doses of IL-2 have potentiating effects. Other cytokines may have opposite effects in that low doses potentiate NMDA-activated current whereas high doses have potentiating effects. Thus, the individual cytokine as well as its level needs to be taken into account in the design of studies.

In the brain, cytokines appear to act principally as neuromodulators rather than as immunomodulators. Studies of cytokines in humans are limited by the fact that peripheral (blood) cytokines are the only readily accessible ones; brain levels can be assessed but would require cerebrospinal fluid (CSF). Studies in rodents have demonstrated that while peripheral cytokine levels may influence the levels of cytokines in the brain, they may not reflect the brain levels, which appear to be very low and difficult to assay. New information indicates that adipose tissue, which is highly enervated, may be a significant source of peripheral cytokines that appear to be proinflammatory. The role of these adipose-tissue-associated cytokines will need to be considered in the design and analysis of future studies.

Cognition

Problems in cognition represent important impairments in persons with CFS. Studies of cognition in CFS must consider a number of factors, including the heterogeneity of the CFS population, the need to identify specific cognitive problems, the impact of psychiatric factors in cognition, and the relationship between cognition and cerebral dysfunction.

Studies of carefully selected CFS subjects, which involved dividing CFS patients into those not having concurrent or previous psychiatric problems and those having them, have shown that intellectual functioning (e.g., global IQ) and simple concentration capacities are intact. Two reproducible abnormalities have been identified in CFS. They are difficulty with complex information processing tasks and reduced speed of processing (e.g., as measured in the PASAT, Paced Auditory Serial Addition Test). Studies of verbal learning and memory demonstrated that the problem in CFS appears to be in learning rather than recall. Once information is learned, it can be recalled. Thus, the problem appears to be in encoding information. Persons without psychiatric co-morbidity appeared to be more impaired in these studies.

In studies of the prevalence of neuroimpairment, it appeared that about one-third of persons with CFS had objective cognitive problems. Depression and fatigue did not appear to be related to neuropsychological performance. The PASAT was the best predictor of neuropsychological problems. In studies trying to distinguish whether CFS represented a medical illness or an atypical presentation of primary depression, of anxiety, or of a somatization disorder, comparisons of persons with CFS, MS, or depression were made by using symptom measures of the Beck Depression scale, such as self-reproach, somatic features, and mood. The symptomatology of CFS and depression differed in these studies.

Magnetic Resonance Imaging (MRI) studies suggested that about one-third of persons with CFS and 10 percent of healthy controls had abnormal white matter, most often in the frontal lobes. If the CFS subjects were divided into those with and without psychiatric problems, 50 percent of CFS patients without psychiatric problems had abnormalities. SPECT studies were more problematic in outcome, but also showed abnormal areas in persons with CFS; these changes also appeared to be more severe in persons with CFS who did not have psychiatric problems.

Functional MRI studies suggested that when presented with a particular task, persons with CFS seemed to activate more areas of the brain, and those areas of the brain appeared to be working harder than similar areas in healthy subjects. This observation might explain the cognitive fatigue reported in CFS. It should be noted that there is no imaging pattern that is diagnostic of CFS.

The cognitive dysfunction observed in CFS was relatively mild when compared to severe dysfunction, such as Alzheimer's disease, but it was disabling to the person. The cognitive dysfunction found in CFS does not appear to be secondary to fatigue or to psychiatric factors, but these factors can exacerbate it. Future studies need to identify subsets and subtypes of CFS populations and need to relate cognition with neuroimaging, with medical factors (e.g., neuroendocrine or immunological findings), and with everyday activity levels.

The methods used to study cognitive problems in one disease have the potential to be translated into studying those in another illness; the approach used to study cognitive changes across the disease spectrum in HIV/AIDS patients was described to provide insights for CFS investigations. Cognitive changes can be measured as mean differences in scores or as a deficit score, that is, an aggregation of scores below a baseline cut-off level. Mean differences assume a common change across most persons with the illness, but these changes may or may not be clinically significant. Deficit scores can detect changes that are more sporadic and focus only on those persons who have changes.

Results from such neuropsychological studies can be used to characterize or diagnose a particular entity, to define subtle changes and determine their impact on function, to use patterns of cognitive changes as clues for defining underlying pathology, or to define predictors and correlates of cognitive change. Initial studies may use a large screening battery, and then as results become available, select tests for specific affected domains. Subsequent tests may use smaller screening batteries to identify persons with problems in specific domains for more extensive testing. However, with this approach, there is the potential to miss some persons with deficits that are not represented in the narrow screening battery.

Several investigational issues face researchers both in HIV/AIDS and CFS. The biological correlates of neuropsychological problems are poorly defined. Defining and clarifying cognitive complaints and translating these into specific domains have provided and should continue to provide additional insights into the underlying pathology. It is important to understand the impact of cognitive problems on patient function to devise coping strategies. The potential interaction of neuropsychological problems with affect or mood disorders needs to be considered.

Methods used in understanding and analyzing data from studies on brain function in depression could provide useful approaches in studying a multicomponent illness such as CFS, as in both cases there is a need to understand the interrelationship between the clinical syndrome, physiological changes, and cognitive deficits. Rather than looking at the results of tests for each component separately, it is possible to use mathematical and visual approaches to depict the data. In studies of patients with depression, data from cognitive scores, mood scores, and functional brain imaging were combined in a neuroplot. Scores from the various cognitive and mood instruments were color-coded and then plotted onto a map of the brain. Thus, changes in speed on the Stroop Test mapped to a different region of the brain than did the number of errors made on the Stroop Test. More important, neuroplots prepared after depressed patients were treated

with Prozac changed to a pattern similar to that in healthy controls. Thus, this approach can be used not only to visualize the interrelationship between functions but also to assess the effects of therapeutic interventions. A neural network approach was also used to map regions from PET scans and cognitive test results. Combining the results of the brain imaging and cognitive testing allowed the network model to identify depression more readily. Thus, these two meta-analytical approaches may allow for the better understanding of individual disorders and for comparisons with overlapping disorders.

Chronic Pain

Pain is an area that has not been as actively investigated in the context of CFS. However, when one considers the minor criteria in the CFS Case Definition, the majority of them are related to pain, thus making pain a significant feature of CFS. There is also a group of disorders that can be characterized as "diffuse pain syndromes", which includes CFS and also FMS, irritable bowel syndrome (IBS), post-infection pain, and post-operative pain. Moreover, there is also a high co-morbidity between CFS, FMS, and IBS, as well as with multiple chemical sensitivity (MCS). The particular diagnosis made for this group of disorders may depend upon the clinical environment in which it is made or on the predominant symptom(s) at the time of diagnosis. The cluster of symptoms seen in these disorders could in fact be explained by mechanisms related to pain. The symptoms also seem to parallel the effects of cytokines; for example, patients who have been treated with interferons for malignancies have a variety of diffuse pain syndromes and many of the symptoms of CFS.

Additionally, there are a number of apparently unrelated medical conditions that have fatigue, pain, and sleep problems as significant symptoms. For example, cancer patients who have been successfully treated with radiation therapy may still have a long term fatiguing state. Infection with *Campylobacter jejuni* may also be followed by months of lingering fatigue. The occurrence of this symptom constellation in diseases with specific known pathologies validates CFS as a clinical entity.

Illness behavior is represented by a complex physiological array that includes fatigue, fever, pain, stress and neuroendocrine abnormalities, with influences by, cytokines, thus suggesting a sharing of common mechanisms across diseases. There is suggestive evidence that much of the symptomatology for diffuse pain symptoms of the type seen in CFS, FMS, and IBS may be mediated by the subdiaphragmatic portion of the vagus nerve. Part of the sex differences seen in pain syndromes may be explained by the structure of the adrenal medulla, which is part of the stress axis and one of the routes that is involved in vagus nerve feedback to the body. Adult female adrenal medulla retains sex hormone receptors, whereas adult male tissue does not.

The perception of pain is influenced by three factors. These are: (a) the intensity and character (e.g., heat, pressure) of the external or internal stimulus that activates nerve receptors; (b) the transmission of sensory information from these receptors to the spinal cord where it is further processed and then sent by ascending nerve tracts to specific sites in the brain; and (c) descending input from the brain to the spinal cord that may either inhibit or facilitate the ascending sensory transmission. An example of this involves studies of the nociceptors, or nerve fibers, that respond to stimuli that are tissue damaging or potentially tissue damaging. Nociceptors are innervated by two types of fibers, alpha-delta myelinated fibers, which transmit very rapidly, and unmyelinated C-fibers, which conduct more slowly and appear to be related to chronic pain.

Studies of pain perception using a combination of heat and capsaicin (the pungent substance of hot peppers) demonstrated how the presence of capsaicin altered the perception of pain. Capsaicin itself creates a warm sensation on the skin but does not cause damage. However, when capsaicin-sensitized skin is subjected to a heat stimulus (43^{o}C) that alone is below the heat pain threshold (typically 45 ^{o}C) the person feels a subjective level of pain that is equal to a heat stimulus (47 ^{o}C) that is above the pain threshold on normal skin. Subtractive PET imaging studies of the two situations (43^{o}C with capsaicin versus 47 ^{o}C on normal skin) indicated that in situations with abnormal sensitized nociceptive processing, the limbic areas of the cerebral cortex and thalamus appear to be involved. Other situations in which pain perception is modified include damage to nociceptors as a result of diabetes. Initially, the nerve injury in diabetes results in pain with normal processing of the information in the spinal cord. However, over time, the processing in the spinal cord appears to change and abnormal information is sent to the brain. Likewise, certain damage to the brain (e.g., the result of a stroke) can alter nociceptive processing, producing the sensation of pain without stimulation of nociceptors or damage to the nociceptors.

Some sex-related differences in pain perception may be explained by observations from PET scan studies that were combined with psychophysical studies. These studies showed that in response to noxious stimuli, the same brain areas were stimulated in men and women, but women have more brain activity than men do. In addition, women rated the stimulus as more intense. This difference was not seen with non-noxious stimuli. A critical area in pain research in general focuses on differentiating sex-related (i.e. biological) influences on pain from those from gender (i.e. sex-role) influences.

Neuroendocrine and imaging studies also suggest that, in FMS, hyperexcitability of the spinal NMDA receptors increases ascending sensory transmission to the brain that enhances pain perception. Persons with CFS usually experience musculoskeletal pain, but they do not show abnormal sensitivity to pressure stimulation at multiple anatomic sites unless they also meet the diagnostic criteria for FMS. Accordingly, individuals with FMS exhibit lower pain threshold levels than persons with CFS who do not meet criteria for FMS; these FMS subjects are also better than CFS subjects and controls in discriminating between high and low intensity stimuli that are presented in random order.

Neuroendocrine and imaging studies suggest a number of similarities and some differences between these syndromes. Thus, both CFS and FMS patients have low levels of cortisol and CRH. FMS patients have low levels of IGF-1 and growth hormone; there is inconsistent data for CFS for these markers. Persons with FMS have low serum levels of serotonin and low CSF levels of serotonin metabolites. Persons with CFS have high plasma levels of serotonin metabolites. FMS is also characterized by high cerebrospinal fluid levels of two factors promoting pain: nerve growth factor and substance P. MRI imaging studies of brain structure suggest that persons with CFS are characterized by a high number of cortical white matter lesions compared to healthy individuals. There are no published MRI studies of brain structure in patients with FMS. Resting state studies of regional cerebral blood flow, using SPECT or PET imaging, have produced different results for persons with CFS and those with FMS. The CFS patient studies generally have not produced consistent results, although two studies found evidence of brainstem hypoperfusion in patients with CFS. One recent British study found that CFS patients show higher levels of blood flow in the thalamus compared to healthy individuals. In contrast, two studies from the same laboratory in the U.S. reported that patients with FMS

show hypoperfusion of the thalamus and/or caudate nucleus during resting conditions. Preliminary evidence from the same laboratory indicates that during exposure to painful pressure stimulation on the right side of the body, healthy individuals display significant increases in blood flow in the contralateral somatosensory cortex, thalamus, and anterior cingulate cortex. However, persons with FMS, as well as those with CFS who do not meet criteria for FMS, show bilateral increases in blood flow in the somatosensory cortex and the anterior cingulate cortex. These findings suggest that both FMS and CFS are characterized by alterations in neural processing of sensory information. Future studies will examine changes in pain perception and regional cerebral blood flow in persons with CFS and FMS when they are stressed before exposure to painful stimulation.

Overall, the physiological approach to treatment of pain has been to eliminate the cause in acute illness, and to treat the signs and symptoms in chronic illness, while trying to understand physiology of the syndrome that could suggest unique therapies. Alterations in nociceptive information processing also need to be considered when assessing the origins and the mechanisms of pain. This type of approach could be carried into investigations and treatment of CFS.

Sleep

The body has a diurnal rhythm of sleep and wake cycles. A pattern of characteristic brain waves for sleep and waking activities can be obtained with electroencephalograms (EEG). Sleep itself can be divided into an orderly series of stages. Aspects of the sleep cycle are described by using the various brain wave patterns identifying rapid eye movement (REM) and non-REM stages. In addition, mood, or how well one feels, also has a cyclic effect throughout a 24-hour period.

For healthy persons, the changes in mood throughout the day are relatively modest. However, for persons with CFS, the level of mood is significantly lower at baseline than for healthy persons and the best time of the day is from 10 a.m. to 2 p.m. or 3 p.m. and after that CFS patients feel significantly worse. Unrefreshing or non-restorative sleep is part of both CFS and FMS. Sleep studies have demonstrated objective evidence for disordered sleep in CFS with the presence of an alpha-delta EEG anomaly, which accounts for the lightness of sleep and the unrefreshing quality of sleep. Studies of cortisol levels in persons with CFS, FMS, and healthy controls demonstrated that cortisol levels fell earlier in the sleep-wake cycle in CFS and FMS subjects than those in healthy controls. Thus, cortisol levels in the sleep-wake cycle in CFS and FMS are lower and shifted in time. Interestingly, the percentage of natural killer (NK) cells also starts to decrease at about 3 p.m. in CFS patients. As part of a Centers for Disease Control and Prevention study, a 17-item sleep questionnaire was administered to persons with CFS and healthy controls; the results indicated that 10 percent of CFS subjects and two-thirds of healthy subjects had good sleep. The tests used in neurocognitive studies are sensitive to sleep deprivation. It was hypothesized that disordered sleep may lead to altered immune functions, which can lead to symptoms. Previous studies in healthy subjects have shown that disruption of deep sleep for as little as a few days leads to tenderness, aches and pains, and fatigue.

Persons with CFS may have disturbed sleep, and some may suffer from depression as well. Antidepressants have been given to CFS patients to relieve symptoms. Individual antidepressant drug classes have different degrees of impact on sleep that may also vary with the sex of the recipient. Information that has been gathered from the study of antidepressants in persons with depression is important to consider when these medications are prescribed in CFS.

Major depression occurs in 10 to 17 percent of the U.S. population; thus, antidepressants are frequently administered drugs. During their reproductive years, women have a two-fold risk over men of having depression. Disturbed sleep increases the risk for depression and, in those who have suffered from depression, increases the risk of relapse and recurrence. Persistent insomnia also increases the risk of suicide. Sleep abnormalities are key symptoms of depression. Even after treatment for depression, about one-third of patients have sleep problems, thus making knowledge of the impact of the various drug classes on sleep important.

Tricyclic antidepressants are inexpensive and widely used. They prolong REM latency, reduce REM sleep and increase total sleep time, but have little impact on depth or quality of sleep. (I.e. they do not enhance deep sleep). Although the side-effect profile does include some daytime sedation, tricyclics do not typically exacerbate sleep disturbances. Selective serotonin reuptake inhibitors (SSRIs), such as paroxitine (Paxil), sertraline (Zoloft), and fluoxetine (Prozac)) also act as REM sleep suppressors, although they are not as potent REM suppressors as tricyclics. More significantly, however, SSRIs increase arousal, intermittent wakefulness, and non-restorative light sleep. Their adverse effects include insomnia, bruxism, and periodic limb movements. Typically, the adverse effects are more pronounced in women, particularly with fluoxetine. With regard to other types of antidepressants, trazodone (Deseryl), a 5HT2 antagonist, decreases wakefulness and increases deep restorative slow-wave sleep. Unfortunately, it is associated with significant daytime sedation. A related compound, nefazodone (Serazone), a 5HT2 antagonist that also has some of the properties of SSRIs (serotonin reuptake inhibition), seems to improve sleep quality (decreased wakefulness and light non-restorative sleep) without causing extreme sedation or agitation.

When asked about their sleep, it is clear that patients are aware of the quality of their sleep, and their subjective reports correlate with laboratory polysomagraphic results. Thus, the sleep laboratory findings have strong relevance to clinical practice. There are a number of reasons for choosing an antidepressant that improves sleep. It not only decreases the need for concomitant medications, but if patients experience improved sleep, they may also be more compliant in continuing medication usage until their depressive symptoms improve.

Animal models of sleep may provide important insights for designing studies to elucidate sleep disorders and devise treatments for them. Studies in mice suggest that tumor necrosis factor (TNF) and IL-1, which are pro-inflammatory cytokines, have a central role in non-REM (NREM) sleep regulation and sleep pathology. The ability of IL-1 and TNF to increase growth hormone release (a sleep-related hormone) and sleep seems to be mediated via GHRH. For instance, antibodies to GHRH block IL-1 induced NREMS responses. A strain of mice (designated *lit*) lacking the growth hormone releasing hormone (GHRH) receptor was used to demonstrate that GHRH also plays a role in modulating NREM sleep In normal mice, acute influenza virus infection increases NREM sleep and decreases REM sleep. In contrast, the *lit* mice have decreased NREMS after viral challenge, thereby implicating the GHRH-receptor in sleep responses induced by viruses. These mice also have a higher mortality after viral challenge and abnormal EEGs. It seems likely that in chronic viral infections, perhaps associated with chronic sleep disturbances, this mechanism may be important.

Additional research is needed about sleep and sleep abnormalities in CFS. There are now technologies that allow sleep to be recorded in the home rather than in sleep laboratories. Treatment trials are also needed to test whether antidepressants do provide benefit in CFS over placebo. Studies of chronobiological treatments such as bright-light, phase-shifting and slow-wave sleep enhancement might also be considered. A new drug that is a TNF-blocking agent has been used for RA and reduces fatigue in RA patients. This type of drug may have therapeutic implications for CFS.

Immunology

A number of observations suggest a role for the immune system or immune modulators in CFS. Several HLA markers appear to be more commonly present in persons with CFS than in the population in general, and these markers are associated with autoimmune diseases. Studies in identical twins also suggest an increased risk of CFS in identical twins. Acute viral-like illnesses appear to precede the onset of CFS in 60 to 80 percent of CFS cases. Immune mediators could directly contribute to the symptoms of CFS (e.g., by allowing reactivation of infections), or they could indirectly contribute to CFS symptomatology by the interaction with the HPA axis, impact on sleep, or interactions with neurotransmitters.

A broad range of lymphocyte markers has been studied in CFS patients and compared to those markers found in healthy subjects. Results from some studies are conflicting, and many studies were hampered by being cross sectional rather than longitudinal in design. There are some indications that markers of T-cell activation are increased during CFS patient flaring. CD3 receptor expression may be reduced; this latter observation might help to explain the poor response to antigens as CD3 is involved in T-cell activation. Low levels of the IgG1 and/or IgG3 subclasses in CFS patients were also seen in several studies. A number of studies also suggest low NK cell function. Some data suggest that the immune system might be constantly activated ("turned on") and immune response blunted by the depletion of necessary cellular enzymes ("exhausted"). Cytokine studies suggest a shift to a TH2 pattern of response in CFS, with expression of the proinflammatory cytokines TNF-a and IL-1. This type of pattern is associated with the humoral side of the immune system, and in combination with proinflammatory cytokines, can be associated with a number of chronic conditions, including autoimmune disease and chronic infection.

There are a number of examples in which the immune system does not properly regulate itself; these include chronic active hepatitis and insulin dependent diabetes. In most individuals a viral infection will be limited, with the body suffering some minimal damage. However, in some individuals, viral infection of islet cells is not limited; the immune system keeps on attacking the cells and the person develops insulin-dependent diabetes. The sickness pattern of loss of appetite, lethargy, etc., that is part of a virus infection is cytokine driven; some of the symptoms of CFS seem to resemble the perpetuation of the virus infection process that has not been shut off.

There is a need for longitudinal studies and for studies that correlate patterns of cytokine expression with illness severity and with the progression of illness over time. Given the heterogeneity of the illness, it is important to study subsets of patients. Collection of specimens needs to be standardized and important confounders such as circadian cycles, menstrual cycle, and patient sex must be taken into consideration. Hypotheses related to the importance of

immune alterations in CFS could be tested by giving immune-based therapies and measuring patient responses.

Psychoneuroimmunological models may also provide insight into the pathogenesis of CFS. During stress, there are changes in the immune system, in levels of hormones in the blood, and in activation of specific areas of the brain. However, in chronic stress models, the more the brain is activated, the more it becomes habituated, and the harder it becomes to activate. This phenomenon is demonstrated by following HPA pathway responses to stress. It is known that when humans are subjected to a stress, the level of cortisol is elevated the first day of the stress; for most people, cortisol is not elevated if the stress is repeated for the next four days, a habituated stress response. However, for some people, cortisol levels will elevate on each of the five days of the stress and these people have more illness and more anxiety. Rather than habituation, there appears to be a sensitization of the brain or a disruption of the regulatory mechanisms of the brain. Studies are needed of persons who habituate to cortisol versus persons who do not habituate to cortisol. In CFS, studies need to be done to determine whether CFS patients' low cortisol levels represent a chronic habituation of the stress response, or if the HPA abnormalities represent a different form of stress response. The mechanistic significance of low cortisol in CFS needs further study. However, the observation of low cortisol in CFS is consistent with the observed chronic immune activation, as cortisol would serve to help down regulate immune activation.

There are a number of concepts from research on multiple sclerosis (MS) that may be relevant to CFS research. The MS disease process begins long before clinical attack. The disease pathology is an autoimmune process. However, the precipitator of attacks/relapse is less clear (e.g., acute viral but not bacterial infections often appear to precede attacks). Immune changes can be measured before an attack, such as increases in inflammatory cytokines, decreases in NK cell numbers, activation of T-cells, and evidence of blood vessel inflammation. After an attack, an anti-inflammatory immune profile is seen. In progressive disease, NK and suppressor cells are defective. In addition, at the time of relapse, immune changes can be detected in certain very specific precursor cells. However, the number of these cells was extremely small; without having the specific target on myelin basic protein, this level of change could not have been detected. There are many MRI changes seen in MS, nevertheless, during many of these times, patients may be asymptomatic. In addition, when looking at parts of the brain not thought to be involved in MS, metabolic abnormalities have been observed in "apparently normal" brain tissues, suggesting that smaller subtle changes could be important.

Several strategies applicable to CFS can be drawn from research approaches used in MS. Diagnostic criteria should be constrained for research purposes. To ensure that patients within a study are uniform, markers should be added for specific studies and, if necessary, rejected if or when experimental findings no longer support their inclusion. Studies should concentrate on early diagnosis, as causal abnormalities are more likely to be detected at that time; long established patients may give false leads both in treatment and in pathogenesis. In terms of therapy, treatment failures in long-established patients may be discouraging, even for therapies that might work early in disease. Treatment studies should avoid "treatment contaminated" patients, that is, persons who have already received therapies, as alterations in markers may be the result of the therapy rather than the disease. Interdisciplinary collaborations should be fostered.

Orthostatic Intolerance/Neurally Mediated Hypotension

Although the description of CFS in the CFS Case Definition does not seem to indicate autonomic system involvement, evidence from the scientific literature provides several suggestions for its potential involvement. This includes (1) the description of myalgic encephalomyelitis cases that suggests autonomic system symptoms; (2) Streeten's description of delayed orthostatic intolerance in 1992 and his proposal that CFS might result from a failure to maintain blood pressure in an upright position; and (3) the studies of Rowe and colleagues in 1995 of neurally mediated hypotension in CFS cases.

Orthostatic tolerance is an autonomic nervous system response that allows people to move from the supine to the upright position without feeling lightheaded, weak, or fatigued. A rapid baroreceptor-mediated reflex is involved to counteract the pooling of blood that occurs in the lower part of the body. This involves vasoconstriction, increases in heart rate, and an approximately twofold increase in noradrenaline levels; blood pressure remains about the same. There are several types of orthostatic intolerant conditions in which this system does not properly operate when a person moves from the supine to the upright position. In orthostatic hypotension, blood pressure decreases, but the heart rate remains about the same; in neurally mediated syncopy or hypotension, the heart rate falls and the blood pressure drops; in orthostatic tachycardia, the heart rate increases, but blood pressure does not change; blood pressure may increase or decrease slightly.

Studies of conditions involving orthostatic intolerance have shown a sharing of features with CFS such as fatigue, female predominance, and viral-like prodrome. Variations in definition of subjects and in test implementation may be contributing factors to differences in experimental findings about the type of orthostatic intolerance in persons with CFS. Nevertheless, orthostatic intolerance conditions may explain aspects of CFS symptomatology and may provide opportunities for therapeutic interventions.

To determine specific cardiovascular changes/deficits that may be associated with CFS, more studies are needed about blood pressure and heart rate during normal daily activities. Investigations are also needed on exercise and cardiovascular change in CFS, variation of blood pressure and heart rate during a 24-hour period, and autonomic outflow during normal daily activities and exercise. Venous end-organ abnormalities need further study, as do baroreceptor reflexes and autonomic control of cerebral blood flow. There are also a number of neurogenic aspects of CFS that need further investigation. These include determining the nature of reflex tachycardia, the basis of the hyperactivation of catecholamines, and whether there are appropriate or blunted vascular responses to them.

Animal models in which there is dysregulation of these systems may also provide additional insights. A transgenic rat model appears to have some aspects of orthostatic hypotension and defective baroreceptor reflexes.

Fatigue, Functional Status, and Disability

Most chronic illnesses have fatigue as a symptom, and studies of fatigue in a range of illnesses can provide approaches or insights for CFS research and therapies. However, fatigue is still a very problematic area in terms of measurement and clinical approach. The main difficulties in measuring fatigue are that it is multidimensional, and there is no "gold standard" against which

to compare measures. In addition, there are differences between acute and chronic fatigue; fatigue may have multiple meanings (e.g., a sense of effort versus anticipatory fatigue), may be the result of both physical and mental tasks, is influenced by both physical and psychological factors, and needs to be distinguished from sleepiness or drowsiness. Aspects of fatigue that can be assessed include behavior (e.g., decline in performance); perception (e.g., proportionality of sense of fatigue to effort); mechanism (e.g., peripheral versus central nervous system); and context (e.g., influence of environmental factors). Domains of fatigue that can be measured include physical/level of activity, mental impairment, functional status/quality of life, and disability. For each of these, both self-report and objective measures are available. Thus, functional status can be assessed by self-report on the Standard Form-36 (SF-36) or measured in the laboratory by the ability of a person to perform specific physical activities (e.g., walking and squatting).

Ideally, measurements of fatigue should be internally consistent and reproducible, should correlate with other measurements of fatigue, and should be sensitive to treatment effects. Self-report measures have limitations in that there is rater bias, they require insight to complete, specific aspects of fatigue may be difficult to distinguish from one another, and fatigue may combine state with trait for those persons with long-standing fatigue. Performance-based measures are more objective and are defined as the inability to sustain the expected power output. In studies of MS, performance and self-report measures showed little correlation and neither alone provided sufficient information on the experience of fatigue. For example, one study used a neuropsychological test as a performance measure of cognitive fatigue in a situation in which there were multiple and repetitive tests. When healthy controls and persons with MS were compared, the healthy subjects had a positive practice learning effect, whereas MS patients did worse on repeated testing. However, both sets of participants felt exhausted, thus demonstrating the lack of concordance between self-report and performance-based measures. It is therefore important to include both types of measures in assessing fatigue.

Impairment of activity is a measure of fatigue. Increased activity is seen as a desired outcome for fatigued patients and as an outcome measure for intervention studies. Actigraphy is a general term for the quantification of activity. It is a behavioral, rather than performance-based, measurement of energy expensive movements, which allows the natural behavior of persons to be assessed in natural settings. A record of activities can be documented around the clock for weeks or months; thus, difficult-to-assess factors, such as restlessness at night, can be measured. Actigraphy allows an assessment of behavior before and after treatment, allows for comparison between subjects, and provides a visual representation to patients of impairments, such as sleep disruption, or of improvements, such as increased activities. Given the cyclic nature of CFS, measurements throughout the day and night and over extended periods of time would provide an important repeated-measures method to assess changes in activity that could be correlated with other biological markers as well as with subjective measures.

Functional status is a subject measure of health status. It may be generic or disease specific. Impairment is a physical or cognitive condition that alters lifestyle. Disability is a state in which impairment precludes a specific function. Thus, a person may be disabled in one area but not in another or may have an impairment that is not disabling. Quality-of-life measures put a value or utility on particular aspects of life. Thus, there is a need to assess fatigue, functional status, and impairment both uniformly and consistently. Part of the estimate of CFS disability is that in the United States about 50 percent of persons with CFS are unemployed. Studies in Seattle of persons with CFS and with FMS showed a degree of disability beyond that which is measured by

the SF-36. Many persons have lost jobs, friends, and significant others and have suffered a decline of standard in their standard of living. Persons with CFS have about twice the average annual per capita medical expenses and have a mean number of 20 medical visits per year.

Fatigue research in cancer may provide insights into research approaches for CFS. Fatigue is a frequent and significant side effect of cancer and cancer treatment, with about two-thirds of patients reporting fatigue. In some cases, fatigue may persist for months or years. It is equally common in men and women and has no age boundaries. The main focus of oncologists has been in relieving pain; however, in response to a survey, cancer patients indicated that fatigue was more important than pain in their daily life. Fatigue is often not reported because it is not asked about or because patients assume that it is part of the illness. Many factors contribute to fatigue in cancer patients, including the tumor itself, pre-existing medical conditions, treatment modalities, infection, depression, pain, sleep problems, and inactivity. Domains of psychosocial functioning are adversely affected by fatigue on a 0 to 10 scale at levels above 5.5. Beyond that level of intensity, virtually every domain of functioning is negatively affected from mood, to ambulation, work, enjoyment of life etc. Below the midpoint of the scale, fatigue has little effect. This circumstance is different than pain, where impairments pile up more gradually. Most patients are given advice on energy conservation such as prioritizing activities, delegating responsibilities, and getting rest and sleep. However, only two categories of intervention have been shown to reduce cancer-related fatigue: moderate exercise and epoetin-alpha therapy. Thus, a walking program was shown to reduce chemotherapy side effects and fatigue. Epoetin-alpha increases hemoglobin levels; with each incremental increase in hemoglobin level, an increased quality-of-life was observed.

Rehabilitation medicine is an area that could provide much assistance and treatment to persons with CFS. It is an area that many physicians are not aware of as a treatment modality; moreover, many therapists are not knowledgeable in the unique needs of CFS patients. Among the rehabilitation medicine specialties, occupational therapy has a key role to play. There are several evaluation instruments, such as the Canadian Occupational Performance Measure, the Role Checklist, the NIH Activity Record, and the NIH Energy Conservation Workbook, that can allow the patient and therapist to identify roles that are important to the patient, and then to prioritize goals and devise strategies to allow patients to achieve the goals most important to them. Speech pathologists may be able to help persons with CFS deal with cognitive problems such as word finding and reading. Physical therapists can assess physical capacity and endurance and can provide interventions to increase these. Rehabilitation professionals can make recommendations for balance of the home and work tasks and for the use of adaptive equipment. There is a need for increased recognition of rehabilitation medicine and for training of professionals in the specific needs of persons with CFS. In addition, research studies are needed to document the effectiveness of rehabilitation medicine as a therapeutic approach.

Issues for Future Research and Consideration in Study Design

There were a number of crosscutting themes throughout the meeting.

CFS patients are heterogeneous. This is recognized by the current case definition, which also encourages the subgrouping and stratification of patients in studies. Patient populations need to be carefully selected and described and indications given in research papers about how the 1994 Case Definition was applied to the study population. The panelists emphasized the need to design studies around specific subgroups of patients.

Need for Longitudinal Studies. CFS symptoms are not static and can change during a day, as well as over days, months, and years. Longitudinal studies and studies considering multiple sampling points are therefore critical. Measurement or characterization of a patient at a single time point is inadequate.

Sampling Methodologies. Sampling points and processing of samples need to be consistent within studies and carefully chosen based on the variables under study. Samples need to be carefully and consistently processed. It is important to consider that samples taken from peripheral blood may not reflect the levels of modulators at their active sites (e.g., in the brain or lymph nodes).

Measurement Methodologies. Measurements of complex functions, such as cognition, need to consider the components of that function (e.g., learning versus recall) and the nature of the impairment (e.g., speed versus accuracy). New technologies, (such as actigraphy) and new analytical tools (such as neuroplots and neural networks) may provide important ways to gather and analyze the complex data that will be needed to study disease mechanisms and pathogenesis.

Potential Importance of Cytokines and Related Neurohormones. While medicine and research studies of necessity divide the body into individual physiological systems, there are in fact many common mediators and cross talk between and among the various bodily systems. For example, IL-1 is named after its immunomodulating functions; however, it plays a role in stimulation of sleep and is involved in stress pathways in that it affects and is affected by CRH. Many of the signs and symptoms of CFS could be attributable to the actions of cytokines; CFS-like symptoms are seen in persons with malignancies who are receiving immunotherapies with cytokines. Pain could explain a number of the symptoms seen in CFS. Studies of the physiology of pain irrespective of cause may provide important insights for understanding pain occurring in specific contexts. Many of the symptoms of CFS could also be caused by disrupted sleep. The role of cardiovascular system dysregulation/dysfunction in CFS symptomatology and pathology needs further investigation.

Dysregulation of control processes/systems was another common theme of the meeting. The consequences of long-term stimulation, aberrant processing of signals, and conditioning of responses were also noted as processes that could provide a mechanistic understanding of the diversity of patient symptomatology, as well as the lack of concordance between subjective symptom report and objective functional measurement. Thus, studies in which animals were subjected to both stress and cytokine administration resulted in changes in the magnitude and duration of the immediate corticosteroid response, as well as alterations to the same stimuli given

at a subsequent time. Biphasic responses to modulators and mediators in which the response, inhibition, or stimulation was dependent on the dose administered were also noted.

Sex and Gender Differences. There are a number of mechanistic clues that might explain the sex and gender differences seen in pain syndromes. These include differences in HPA axis regulation, differences in neural processing, differences in sleep architecture, and differences in clinical responses to drugs.

Overlapping Syndromes. There are a number of syndromes that overlap with CFS, such as IBS, FMS, and MCS. Knowledge gained about one may provide insights for the others; in addition, further research may determine whether these syndromes represent a continuum of related human illnesses rather than being individual entities. Conversely, there are a finite number of symptoms that can occur in an affected organ or organ system; thus, sharing of symptoms may not imply sharing of mechanisms. Interdisciplinary/multidisciplinary studies are needed to address the complex mechanisms that cross physiological systems and research disciplines.

SUMMARY. CFS is a complex multisystemic, multifactorial illness. Its unique aspects and pathogenesis need further investigation and illumination; studies of overlapping symptoms and pathogenic mechanisms from other diseases/disorders may provide insights into the biological basis for this illness.

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October 23-24, 2000

Topic 1: Neuroendocrinology

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Topic 6: Orthostatic Intolerance/Neurally Mediated Hypotension

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Topic 7: Fatigue, Functional Status, and Disability

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Appendix 1 Financial sponsors of the conference

Centers for Disease Control and Prevention

National Institutes of Health:

- Office of Research on Women's Health
- National Institute of Allergy and Infectious Diseases
- National Institute of Neurological Disorders and Stroke
- National Institute of Arthritis and Musculoskeletal and Skin Diseases
- National Institute of Nursing Research
- National Center for Complementary and Alternative Medicine
- National Institute of Mental Health

Appendix 2 Conference Speakers

Overview of Conference and Conference Goals: Donna J. Dean, Ph.D., National Institutes of Health, and Anthony Komaroff, M.D., Harvard University, Conference Moderator

A Patient's Perspective: Ms. Bernice Soohoo Lee, Oakland, California

A Community Physician's Perspective: David Bell, M.D., FAAP, Lyndonville, New York

Topic Session 1: Neuroendocrinology: CFS Investigator, Philip W. Gold, M.D., National Institutes of Health—Subject Experts: Mark Opp, Ph.D., University of Texas at Galveston; Steve Zalcman, Ph.D., UMDNJ-New Jersey Medical School

Topic Session 2: Cognition: CFS Investigator, John De Luca, M.D., UMDNJ-New Jersey Medical School, Kessler Institute of Rehabilitation—Subject Experts: Yaakov Stern, Ph.D., Columbia University; Roderick Mahurin, Ph.D., University of Washington

Topic Session 3: Chronic Pain: CFS Investigator, Jon Levine, M.D., Ph.D.,University of California, San Francisco—Subject Experts: Kenneth Casey, M.D., University of Michigan; Laurence Bradley, Ph.D., University of Alabama

Topic Session 4: Sleep: CFS Investigator, Harvey Moldofsky, M.D., University of Toronto—Subject Experts: Roseanne Armitage, Ph.D., University of Texas, Dallas; James Krueger, Ph.D., Washington State University

Topic Session 5: Immunology: CFS Investigator, Nancy Klimas, M.D., University of Miami—Subject Experts: Bruce Rabin, M.D., Ph.D., University of Pittsburgh; Jerry Wolinsky, M.D., University of Texas, Houston

Topic Session 6: Orthostatic Intolerance/Neurally Mediated Hypotension: CFS Investigator, Roy Freeman, M.B., CH.B., Beth Israel-Deaconess Medical Center—Subject Expert: David Averill, Ph.D., Wake Forest University

Topic Session 7: Fatigue, Functional Status, and Disability: CFS Investigator, Dedra Buchwald, M.D., University of Washington,—Subject Experts: Lauren Krupp, M.D., SUNY, Stony Brook; Warren Tryon, Ph.D., Fordham University; Steven Passik, Ph.D., Community Cancer Care, Inc.; Gloria Furst, OTR/L, M.P.H., Clinical Center, NIH