

NEURO-IMMUNE MECHANISMS AND CHRONIC FATIGUE SYNDROME:

*Will understanding central mechanisms enhance the search for
The causes, consequences, and treatment of CFS?*

A Scientific Workshop Sponsored by the
NIH Office of Research on Women's Health and the Trans-NIH Working Group for Research on
Chronic Fatigue Syndrome
June 12-13, 2003
Bethesda, Maryland

The impetus for this workshop was the need to attempt an explanation for the diverse and often conflicting research literature on Chronic Fatigue Syndrome (CFS). Although research to date has led only to the conclusion that there is neither an identifiable cause nor a cure for CFS, there is a body of evidence that suggests alterations in both the immune and neurological systems. Thus, scientists of diverse disciplines from within the NIH intramural research community as well as distinguished extramural experts were convened to explore the mechanisms by which hormones, cytokines, and other mediators act as intermediaries between the brain and other body systems. These scientists also explored how new methodologies developed for the neurosciences, e.g. imaging, genomics, could be used to study the central and peripheral actions of these mediators to better understand CFS other multisystemic illnesses of unknown origin, many of which overlap, that are studied at the NIH and are important to women's health and gender studies.

Background

It has been posited that the central nervous system (CNS) should be studied in CFS and related disorders not only because fatigue (the principal symptom of CFS) may be understood in terms of CNS physiology and other important symptoms (such as pain, sleep disturbance, and cognitive dysfunction) are also best understood in terms of CNS function, but also because the brain is the organ that controls and regulates all action and interaction between the diverse body systems affected in CFS as well as the input from the external environment. Thus, it could prove an integrative model in which to explain female predominance, acute onset, uniformity of symptoms, absence of prominent findings on physical examination, substantial disability, and altered perception that exist in CFS and the multiple conditions with which it overlaps, e.g. Temporomandibular Muscle and Joint Disorders (TMJ), chronic pain, Fibromyalgia (FM), Irritable Bowel Syndrome (IBS). Such a model must include elements from multiple fields and domains, and should focus on understanding the relationship between objective findings and the symptoms and suffering experienced by patients.

With these issues in mind, the Office of Research on Women's Health and the Trans-NIH Working Group for Research on Chronic Fatigue Syndrome sponsored this scientific workshop, chaired by Drs. Dedra Buchwald and Leslie Crofford. The meeting took place June 12 and 13, 2003, in Bethesda, MD.

Purpose of this Scientific Meeting

The group was charged with exploring the following questions in this workshop:

- Can CFS and other related disorders be understood as disorders of central nervous system physiology?
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- If CFS is a disorder of the CNS what methodologies are available to investigate disorders of central nervous system physiology?
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- Are there therapeutic approaches that specifically target central nervous system physiology that should be applied to CFS?

Structure and Process

The Workshop consisted of seven sessions over a period of two days. Each session was introduced and moderated by a chairperson. Discussion was encouraged among presenters and participants throughout the meeting. Session 1 consisted of a complete discussion of the clinical manifestations and hypotheses regarding the etiology and pathogenesis of CFS. Session 2 provided a thorough understanding of the role of the HPA axis in CFS including health consequences of a dysregulated stress response, augmentation of immune function, and effects of antidepressants to evaluating immune functioning in CFS patients. Session 3, which was intended to focus on the role of the autonomic nervous system (ANS) actually highlighted the complex interactions between CNS and the ANS activity in exercise, insomnia, depression, and cardiac function. The need to see the nervous system, indeed the entire body, as a complex and unified whole became evident. Session 4 focused on cytokines, sleep and the CNS. It is quite compelling how the sleeping and waking brain relate to regulatory functions involving cytokines, neuroimmune, and neuroendocrine functions.

Session 5, on day two, focused on the application of CNS methodologies to the investigation of CFS, e.g. genetic studies among families, genomics-biomarker discovery focusing on psychoneuroimmune factors, examining the brain circuitry in the regulation of physical and affective states, and the need to consider hormonal status in the study of any of these multisystemic conditions. Session 6 focused on CNS therapeutics and a number of promising pharmacological and non-pharmacological treatment approaches were considered. The final session (Session 7) was a summary of findings from the meeting and an opportunity to address model design of the CNS hypothesis to test CFS. Several ideas were put forward. The overall conclusion from participants was that sufficient evidence had been presented, and appropriate tools were available to study CFS as a disorder of the CNS. The only caveat was that this endeavor may prove to be a costly and time intensive undertaking.

Major Themes

- CNS hypotheses to explain CFS and its many variations should be generated and tested.
- A common pathway, as evidenced by familial studies, may underlie CFS, IBS, and FM, and other similar conditions.

- When considering complex diseases such as CFS, multiple genetic, developmental, and environmental factors need to be considered, as well as response of the host to chemical, behavioral, psychological or environmental triggers.
- CFS and similar conditions must be studied in non-linear integrative models. These syndromes often involve a form of dysautonomia, a condition in which altered function of ANS adversely affects health. Attempts to separate mind from body, psyche from soma, and psychiatry from medicine do not succeed when treating dysautonomias, because these conditions are integrative, mind-body, multi-disciplinary disorders. A new discipline of scientific integrative medicine presents a promising approach.
- Chronic stress has been found to suppress immunity, and CFS patients often report that stress worsens their symptoms. Stress can affect CFS in many ways and these issues need to be studied using a multi-factorial approach. The study of HPA axis physiology and its relationship to the central and peripheral symptoms associated with CFS and related syndromes could inform the understanding of vulnerability to these syndromes, types of triggering events, specific symptom profiles of individual patients and groups of patients, and approaches to therapy.
- Current knowledge links certain cytokine/immune/neuroendocrine functions to the sleeping-waking brain. Further related information is expected to lead to a better understanding of how the operations of the brain affect the symptoms of CFS and similar conditions.
- Because CFS is a multi-factorial, multi-system disease, researchers and clinicians will need to employ pharmacological and non-pharmacological treatments using a multi-disciplinary approach.

Methodological and Other Issues still to be resolved

- CFS studies must be longitudinal and conducted in multiple centers with sufficient subject numbers for statistical power and must be of sufficient duration to account for cycles of remittance and relapse.
- Methodological limitations, such as sampling time, specimen shipping conditions, processing methods and preservation, must also be standardized.
- Useful phenotypes for the symptoms of CFS must be developed and defined so that they can be measured accurately.
- There remains a need for the development of an animal model for CFS.

- Researchers should take advantage of the newer scientific methods and techniques that can be applied to provide immediate insights into the symptoms of CFS Use of these approaches will ensure that the projects undertaken are interdisciplinary in nature.

Unexplained clinical Parameters include:

- Variability in clinical manifestations
- Specific symptoms (e.g., exercise intolerance)
- Female predominance
- Altered perception/belief
- Correlates of acute onset
- Exposures – medical histories remain vitally important as key element of how to explain chronic diseases

Publication of the Proceedings of this Scientific Meeting

A proceedings book is being prepared that will include all of the sessions from this scientific meeting. This publication should be available sometime in 2004. Check this web site for updates.

For more information about Chronic Fatigue Syndrome, click on these suggested links:

- Chronic Fatigue and Immune Deficiency Syndrome Association of America:
www.cfids.org
- Centers for Disease Control and Prevention:
www.cdc.gov/ncidod/diseases/cfs/defined/index.htm
- NIH Office of Research on Women's Health: www4.od.nih.gov/orwh/cfs-newhome.html