

Immunologic Aspects of Chronic Fatigue Syndrome

Report on a Research Symposium Convened by The CFIDS Association of America and Co-Sponsored by the US Centers for Disease Control and Prevention and the National Institutes of Health

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Abstract

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

pated in this meeting. Data suggest that persons with CFS manifest changes in immune responses that fall outside normative ranges, but current research does not provide definitive evidence on whether these immune abnormalities are a cause or result of the illness. It has become clear that CFS cannot be understood based on single measurements of immune, endocrine, cardiovascular, or autonomic nervous system dysfunction. This panel encourages a new emphasis on multidisciplinary research into CFS.

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Introduction

Chronic fatigue syndrome (CFS), also known as chronic fatigue and immune dysfunction syndrome (CFIDS) and myalgic encephalomyelitis, is a serious health concern. A study by DePaul University estimates

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CFS prevalence at approximately 422 per 100,000 adults in the USA [1]. This means as many as 800,000 people nationwide suffer from the condition. Studies show that 85–90% of people with CFS have not been diagnosed and are not receiving appropriate medical care for their illness. It is nearly twice as common in women as men. To put CFS prevalence into perspective, systemic lupus erythematosus affects 50 per 100,000, multiple sclerosis affects 104 per 100,000, and rheumatoid arthritis affects 1,022 per 100,000 American adults.

CFS affects adults, adolescents and older children of all races and socioeconomic groups. Additional data from the DePaul study found a significantly increased prevalence in minorities and persons in lower-income brackets, two populations that have not been previously recognized as being at greater risk than non-minorities for CFS, and which are generally underserved by the medical community. Of all the people with CFS identified in this study, only 10% had been previously diagnosed, lending extra impetus to efforts to increase knowledge and awareness of CFS.

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

To be diagnosed with CFS, a person must meet the following 1994 International Research Case Definition criteria [2]:

- *Unexplained persistent or relapsing fatigue for at least 6 months' duration* that is of new or definite onset, not the result of ongoing exertion, is not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social, or personal activities *and*
- *Four or more of the following eight symptoms*, persistent or relapsing, for at least 6 months: impairment of short-term memory or concentration; sore throat; tender cervical or axillary lymph nodes; muscle pain; multi-joint pain without joint swelling or redness; headaches of a new type, pattern or severity; unrefreshing sleep, and postexertional malaise lasting more than 24 h.

CFS seems to be a multi-system disorder. The etiology and pathophysiology of the syndrome is unknown. However, there have been a number of studies suggesting an involvement of the immune system in the pathophysiology of CFS. This symposium was designed to explore the possibility of an association between the immunologic system and CFS and, if so, what that association might be.

Following one day of presentations by experts, an independent panel composed of well-respected researchers and practitioners in the fields of biostatistics, immunology, infectious disease, rheumatology, endocrinology, psychiatry, exercise physiology, epidemiology, pediatrics, and internal medicine, as well as two patient representatives, weighed the scientific evidence and developed a draft statement in response to the following five key questions:

1. What is the evidence that there is dysregulation of the immune system in CFS?
2. What is the evidence of the involvement of infectious agents in CFS?
3. Are there examples or models of immune dysfunction that could lead to the symptoms of CFS?
4. What can we learn from the existing data on interactions among the immune system, HPA axis, and autonomic nervous system about the clinical presentations of CFS?
5. (a) What are the recommendations for future research? (b) What are the recommended opportunities for research collaboration? (c) What methodological barriers are there to the careful study of these recommendations?

This statement was prepared by a panel of experts, based on (1) presentations by investigators working in areas relevant to the consensus questions during a 1-day scientific court session; (2) questions and statements from conference attendees during open discussion periods that are part of the scientific court session, and (3) closed deliberations by the panel during 1½ days. This statement is an independent report of the panel and is not a policy statement of The CFIDS Association of America, the National Institutes of Health or the Centers for Disease Control and Prevention.

The CFIDS Association of America

This symposium was convened by The CFIDS Association of America, with co-sponsorship from the National Institutes of Health Office of Research on Women's Health and the Centers for Disease Control and Prevention.

Founded in 1987, The CFIDS Association of America is the largest and most active charitable organization dedicated to conquering CFS. The Association has invested over USD 12 million in education, public policy, and research programs in its efforts to bring an early end to the suffering caused by CFIDS, including more than USD 3.4 million in grants to individual CFIDS researchers.

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

1. What is the evidence that there is dysregulation of the immune system in CFS?

In published reports on the immunologic evaluation of patients with CFS, there is substantial evidence that a large proportion of patients has some immunologic abnormalities (i.e., differences from control data), including decreased natural killer cell activity, an increase in the percentage of T cells expressing activation markers, decreased lymphocyte stimulation by certain mitogens and soluble antigens, and increased production of certain pro-inflammatory cytokines. The humoral immune system has also shown frequent abnormalities, including hypergammaglobulinemia, increased titers of various antibodies, and the presence of immune complexes. These changes support the conclusion that dysregulation of cellular and humoral immune response are associated with CFS.

However, the ability to understand the role of these changes in the pathogenesis of CFS is constrained by several major limitations in many of the studies reported to date: (a) most reported studies of the immune system in CFS have a cross-sectional design and there is a paucity of longitudinal data; (b) the CFS patient populations studied have been highly heterogeneous, with considerable variation related to gradual vs. sudden onset of disease and epidemic or non-clustered occurrence; (c) variable timing of assessment in relation to onset of symptoms, and insufficient documentation of the possible relationship between abnormalities and timing of assessment; (d) considerable heterogeneity in the methodologies used to assess immunologic parameters, with little indication of quality assurance or standardization, and (e) a paucity of data to associate the type or magnitude of immunologic abnormalities with the nature or severity of symptoms of CFS.

Inadequacies in the research to date limit inferences about the relationship of immune dysregulation to the eti-

ology of CFS. However, the pattern of immune abnormalities suggests that immunologic factors may contribute to the pathogenesis of the chronic fatigue and other symptoms. It seems plausible that the overproduction of some pro-inflammatory cytokines contributes to the fatigue. The recent demonstration of activation of the 2-5A synthetase pathway (associated with interferon- α signal transduction) in some CFS patients provides support for this hypothesis.

2. What is the evidence of the involvement of infectious agents in CFS?

Direct and indirect evidence exists that infections play a significant role in the pathogenesis of CFS for certain patient subsets. This probably applies preferentially to persistent active infections, and no single agent is common to all patients. Some infections may occur epidemically or endemically. For instance, the Lake Tahoe data may suggest an infectious epidemic of Epstein-Barr virus (EBV), while Coxsackie virus activity in CFS cases in Great Britain may suggest endemic reactivation of the virus. The ability to evaluate published data is limited in part by the use of inadequate techniques to identify reactivated infections in viral persistence. Multiple methods should be used simultaneously, e.g., serology for screening and antigen capture, DNA/RNA activity, or isolation of the infectious agent for verification.

The strongest evidence for involvement of infectious agents in the pathogenesis of CFS when at least two of the techniques are used comes from the finding of persistent activity of EBV and/or HHV-6 in up to 30% of CFS patients. Some evidence – in part endemic – exists for CMV, Coxsackie, Lyme disease and Q fever. Similar to immunological studies, the heterogeneity of the case material, lack of longitudinal studies – and, to a certain extent, inadequate documentation of case history and techniques applied – limit the ability to relate infections, immunologic and clinical data to etiology and pathogenesis.

The infectious theory of CFS fell out of favor for a period of time. The reasons for this include the inadequacy of techniques to diagnose active and persistent infection, the multiplicity of organisms that may be involved in the pathogenesis of CFS and the cross-sectional design of studies without adequate follow-ups.

The search for infectious agents in CFS patients should be initially guided by diagnosis of specific organ symptoms and the detection of circulating antibodies and antigens to the agents that have been implicated in CFS.

3. Are there examples or models of immune dysfunction that could lead to the symptoms of CFS?

There are a number of epidemiological, pathological and naturalistic models that have been used in CFS research. Furthermore, it is often assumed that viral infections or cytokine abnormalities are a necessary part of the syndrome, although this is not certain. However, there has been no comprehensive model for the study of immune dysfunction in relationship to the symptoms of CFS and related disorders. Nevertheless, there are a number of paradigms in which either viral infections or cytokine administration cause changes which appear to trigger, in one form or another, some of the signs and symptoms of CFS.

Unfortunately, models used to study CFS demonstrate a number of methodologic shortcomings that must be remedied to enhance future studies. Even so, there seem to be sufficiently strong associations between the observations in models and CFS symptoms to suggest that this could be advantageously pursued from a heuristic point of view. A number of the models discussed in detail seem to be promising.

Based upon studies presented at this Symposium and investigations described in the literature [3], we have identified a number of experimental models for studying various aspects of CFS. Most studies have not been hypothesis driven. We endorse the need to design future studies based on specific hypotheses and using appropriate methodologies.

The strength of this approach is that it would not simply generate new findings, but hopefully would generate replicable findings and, most importantly, provide results to either support or reject the hypothesis. These studies should also seek to employ methodologies that are reproducible across investigative sites over time. Given the large normal variability in immune function parameters, we recommend that appropriate standardization of methodologic procedures with quality assurance and reduction in extraneous variables be established to allow replication of experimental results. In particular, we would recommend that longitudinal studies be pursued whenever possible.

A good experimental model, in our opinion, should: be theory-driven and involve hypothesis testing; define outcome measures thoroughly; carefully specify methods for reproducibility by other laboratories; utilize well-characterized and homogeneous subject populations when possible; employ appropriate control or comparison groups; generate verifiable, a priori predictions with appropriate outcome measures, and be adequately powered. All ef-

forts should be made to use models that are testable by different investigators and can generate additional novel hypotheses.

EBV has been the most studied experimental model to date. A subset of individuals with acute mononucleosis go on to develop a more chronic disease state with manifestations closely similar to CFS. In addition, those in apparent remission may experience reactivation of the infectious agent. This has proven to be a powerful prototypic model for CFS, and has more recently been expanded to include other infectious agents. These include: cytomegalovirus, Borna virus, HHV-6, -7 and -8, enteroviruses, rickettsia, Ross River virus, Q fever, Lyme disease, and retroviruses, including the novel JHK agent.

The Dubbo cohort study exemplifies a post-infectious fatigue model that demonstrates many methodological strengths. This study specifically examined post-infective fatigue in relation to three infectious disease models (EBV, Q fever and Ross River virus) in a prospective, longitudinal fashion. Patients were characterized clinically and virologically. Assessments were performed regularly over an extended period. This should allow for correlation between symptoms of fatigue and specific immunological parameters in these three chronic infectious diseases.

Another intriguing model is the JHK virus, which suggests the possibility of synergistic infection by more than one viral agent. This is a retrovirus that appeared as a co-infection with EBV in 1 subject with CFS and has recently been propagated in a cell line.

The possible reactivation of EBV and rise in a specific EBV enzyme following exposure to a stressor may provide a model for infectious agent reactivation and CFS. In patients who go on to develop the symptomatology of CFS, possible pathophysiological measures can be examined, such as changes in functional MRI and regional cerebral blood flow. In addition, using specific techniques, we can measure the effects of viral protein on both the up- and down-regulation of cytokines.

Infection with *Borrelia burgdorferi* (Lyme disease) has been clinically associated with CFS in some patients. One study has examined the relationship between Lyme and CFS-like symptoms. Although no specific immunological parameters were measured in this study, these investigators used a treatment intervention model with antibiotics to test this infectious disease hypothesis. Although not an ideal design, the fact that many patients did respond to treatment with reduction in symptoms indicates that this may be a model for alleviation of symptoms in CFS. Such studies should preferably employ adequate control groups.

An additional post-infection model is the Guillain-Barré syndrome, in which antibodies to the infectious agent(s) rely on molecular mimicry of a cerebrospingolipid as the pathogenic agent, rather than an increased level of cytokines. However, Guillain-Barré may be more characteristic of the peripheral manifestations of CFS. While viral models with neurological effects are of interest, those that do not exhibit profound fatigue as a major symptom appear to be of limited value for research on CFS.

Abnormal levels of several cytokines have been associated with CFS. Some of these have been used therapeutically in clinical situations, such as in the treatment of various neoplastic or infectious disorders. In one study, administration of IFN- α triggered fatigue in more than 70% of patients, as well as a depression-like syndrome. In addition, this model was also able to produce CFS-like symptoms, including cognitive deficits, possible appetite disturbance, muscle and joint pain and sleep disturbance. These observations suggest that changes in response to administration of cytokines may be a useful model for studying CFS. Advantages of this manipulation also include the ability to utilize a control group (i.e. patients who are untreated) plus the capacity to collect cerebrospinal fluid and possible tissue/brain biopsy samples, as well as to conduct functional brain imaging.

4. What can we learn from the existing data on interactions among the immune system, hypothalamic-pituitary-adrenal (HPA) axis, and autonomic nervous system about the clinical presentations of CFS?

Investigators in various disciplines have brought their collective expertise and differing perspectives to elucidate the complex pathophysiology of this disorder. For instance, immunologists have used a measure of the body's early defense system, natural killer cell activity, as a potentially reproducible parameter. Other measures that have been utilized include markers of T-cell activation and immune system dysregulation. In particular, it has been hypothesized that a shift in immunity from a cell-mediated Th1 bias to a predominantly antibody-dominated Th2 response, associated with slightly elevated levels of circulating immune complexes and mildly positive ANA values, is characteristic of this condition. This is also evidenced by increased IL-4 production and manifest by increased allergy symptoms, as well as some evidence of autoimmune phenomenon in patients with CFS. Changes in immunoglobulin levels, however, have failed to teach us much about the etiopathology of this illness.

It is well established that the immune and endocrine systems are inextricably linked through various mecha-

nisms and interrelated feedback loops. There is compelling evidence that a variety of cytokines can stimulate the HPA axis, and may also exert a positive influence on the sympathetic nervous system. Conversely, activity of the HPA axis leads to down-regulation of cytokine production. These complex interactions render study of any single component difficult to interpret in the absence of evidence regarding other parts of the system. There is some evidence that CFS is associated with an under-active HPA axis, although this is not universally found. However, if this indeed is present, it could, at least in part, lead to up-regulation of the immune system and an increase in circulating cytokines. It is also possible that central hypoactivity of the HPA axis, at the level of the hypothalamus, can negatively influence sympathoadrenal activity. To complicate matters further, reproductive hormones may also exert an influence on inflammatory cytokine production, and may help to account for the clear gender differences in CFS prevalence.

It has been suggested that external stressors may perturb the relationships among these three components, and lead to long-term chronic changes. This is particularly the case if the external stressor has certain defining features, including perceived uncontrollability and unpredictability, compounded by lack of social and personal support. This in turn may lead to recrudescence of a previous inflammatory response, which may feed forward into the CNS. The long-term sequelae may be CNS effects and myalgia symptoms of a primarily cytokine response. The source of the cytokines may be central, and measurement of peripheral cytokines may not reflect neuronal responsiveness.

Little is known about the influence of the immune or endocrine systems on autonomic function in CFS. Although orthostatic intolerance is more common in CFS than in healthy controls, there is no known link between this and immune or endocrine dysfunction. Neither is there evidence of widespread pandysautonomia in the CFS population.

5. (a) What are the recommendations for future research?

Data from several cross-sectional studies suggest that a number of persons with CFS manifest changes in immune responses that fall outside normative ranges. People with CFS constitute a heterogeneous population, in terms of the number and severity of symptoms at a given time. Because of this diverse presentation, the panel recommends the implementation of longitudinal studies that include the following key elements:

- The use of adequate numbers of subjects to assure robust statistical power.
- The appropriate application of statistical methodology.
- Well-characterized cases and controls stratified by gender, age, type of onset (e.g., sudden vs. gradual, viral vs. stress), duration of symptoms, other concurrent clinical conditions, geographic occurrence (cluster vs. isolated cases), and therapeutic regimen.
- Blood samples drawn at specified times, particularly with regard to chronobiology and the menstrual cycle, and with minimization of the pain and stress experienced during blood sampling.
- Assays designed to measure immune function: (a) natural killer cell activity; (b) percentage of peripheral blood lymphocytes expressing activation markers; (c) pro-inflammatory cytokines and soluble receptors; (d) Th-1 and Th-2 responses; (e) activity of the 2-5A synthetase pathway, and (f) serum immunoglobulin levels.
- Selected measures of autonomic nervous system and neuroendocrine functioning.
- Functional magnetic resonance imaging studies.

Because data from several serological studies suggest that reactivation of latent infectious agents may play a role in the genesis of CFS, further studies are needed to demonstrate:

- The presence or absence of viral/microbial genetic materials from multiple, prospectively collected specimens.
- The association of each infectious agent with the immunological profile seen in CFS, with attempts made to link these findings to symptoms and functional disability.

Despite our present inability to identify a single specific etiology responsible for all CFS cases, intervention trials in well-defined subsets of the CFS population may identify useful therapeutic modalities. These therapies would be designed to improve the quality of life of CFS patients while also adding to our understanding of the etiopathophysiology of the illness. Possible candidates for such intervention trials include anti-inflammatory cytokine antibodies or soluble receptors, antivirals, antibiotics and immunomodulatory agents.

(b) What are the recommended opportunities for research collaboration?

Unfortunately, research on the natural history, etiology, pathogenesis, and treatment of CFS has been limited by an emphasis on single-discipline investigations. CFS research to date has been characterized by the separation

of infectious, immunological, endocrine, neurological, cardiovascular, and psychological investigations of the CFS population. In addition, interactions between researchers and clinicians from these diverse disciplines have been inadequate to generate unifying hypotheses to confront the complex challenge of this illness.

This panel encourages a new emphasis on multidisciplinary research into CFS, involving the collaboration of specialists from multiple fields such as immunology, microbiology and infectious diseases, neurology, endocrinology, electrophysiology, psychology, epidemiology and rehabilitation. The use of interdisciplinary, multi-site (including international), longitudinal studies to explore potential links between the variations noted in CFS patients' immune, neuroendocrine, and cardiovascular systems is critical to developing an understanding of relationships among causal factors, symptom progression, and recovery.

In addition, the field of CFS research may benefit from collaboration between clinicians and researchers familiar with distinct subpopulations, such as children, adolescents, underserved populations and ethnic groups, pregnant women or post-menopausal women. For example, international and trans-cultural cooperation among clinical researchers and epidemiologists may help to identify the features of CFS in other cultures and environments. Furthermore, including children and adolescents in studies of pathophysiology may help overcome the problem of confounding factors, and offer the opportunity to document the early onset of a primary infection that may lead to CFS. Finally, investigating CFS in the different stages of a woman's life, including pregnancy, is important not only to address the unmet needs of this population, but also to better describe the impact of reproductive hormones and pregnancy on CFS. In addition, the outcome of perinatal exposure of infants to a woman with CFS has yet to be evaluated through research.

(c) What methodological barriers are there to the careful study of these recommendations?

Three primary methodological barriers impair the investigation of CFS: poor study design, the heterogeneity of the CFS population, and the lack of standardized laboratory procedures and resources.

The quality of previous CFS research study design is to some degree indicated by the fact that meta-analysis of CFS research is nearly impossible. Obstacles to meta-analysis include both lack of information about the methodologies employed, and multiple differences in methods of subject recruitment and classification, clinical definitions applied, the specifications of clinical and laboratory

tests, and outcome measures used. The panel strongly recommends that new studies not only be hypothesis-driven, but that their design facilitates replication across different research settings.

A key issue in CFS study design is the need for larger, carefully defined populations. Such studies enable the identification and characterization of subgroups within the heterogeneous CFS population. Identifying such subgroups may enhance future research of pathophysiology and may lead to the development of therapeutic interventions. However, studies of more homogeneous populations may be more likely to lead to reproducible results. Multi-site studies may produce designs with adequate statistical power.

In order to recognize factors significant to CFS subgroups, all subjects and controls must be well characterized according to variables such as: circumstances of onset; age, gender, ethnicity, and socioeconomic status; age at illness onset; duration of illness; reproductive health status; co-existing diagnoses; functional status at time of investigation; current or past medications and therapies used by the subject; adiposity; and psychological status and history.

CFS research is complicated by the variability in individual patients' laboratory results. The findings reported for CFS patients may vary with their health status and can also sometimes be found in control populations. Another source of this variability may be a non-specific, inflammatory immune response to one or more of the triggers responsible for CFS. In addition, it may be difficult to differentiate between results found in CFS patients and controls because latent infections prevalent in high percentages of healthy populations could also be linked to the etiology of CFS.

These confounding factors can only be overcome through establishing detailed, standardized methodology that differentiates between latent infections that are normally present and those that are more frequently activated and associated with symptoms of CFS. Standardization of laboratory methods will also help to ensure replication of results. Furthermore, the addition of resources such as blood, serum and tissue repositories will enhance future studies by providing a source of specimens from well-characterized patients for use with new investigative techniques.

It is our obligation to identify and overcome the methodological barriers outlined above. It is well within our abilities to accomplish this through interdisciplinary cooperation and collaboration.

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References

- 1 Jason LA, Richman JA, Rademaker AW, Jordan KM, Plioplys AV, Taylor RR, McCreedy W, Huang CF, Plioplys S: A community-based study of chronic fatigue syndrome. *Arch Intern Med* 1999;159:2129-2137.
- 2 Fukuda K, Straus SE, Hickie I, Sharpe M, Dobbins JG, Komaroff A: The chronic fatigue syndrome: A comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med* 1994;121:953-959.
- 3 The literature review used by the evaluation panel is available at <http://www.cfids.org/about-cfids/immuneliterature-review.asp>