Chronic Fatigue Syndrome Research
Definition and Medical Outcome Assessment

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On 18 to 19 March 1991, the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Mental Health (NIHM) workshops to improve the reproducibility of results and precision of tests in chronic fatigue syndrome (CFS) research. The meeting was attended by about 100 scientists, science administrators, and patient support group representatives. General internists, infectious disease specialists, rheumatologists, psychiatrists, and other specialists shared their research experience to grapple with the problems associated with investigating the causes and consequences of CFS.

Chronic fatigue syndrome has as its dominant feature fatigue of unknown etiology. Other symptoms may include weakness, fever, sore throat, painful lymph nodes, arthralgia, memory deficits, confusion, postexertional malaise, headache, and sleep disturbance (1). In 1985 at the first NIAID workshop, it was agreed that the greatest obstacle to CFS research was the lack of an objective case definition. Because CFS lacks pathognomonic signs and shares some symptoms with some psychiatric disorders, case definition remains a pivotal problem.

Through a collaborative effort spearheaded by the Centers for Disease Control (CDC), a working case definition (Table 1) was developed for research purposes and was published in February 1988 (2) followed by a clarifying letter that appeared later that year (3). Results of a similar effort to reach a consensus on case definition in the United Kingdom were published in 1991 (4), and a set of similar criteria was developed for an epidemiologic study conducted in Australia (5). Participants in all three efforts attended the NIH workshop.

The purposes of the workshop were 1) to review the collective experience of investigators in the United States who have been using the CDC criteria for case definition in their research and, if necessary, to make recommendations concerning further modification and 2) to discuss approaches to assessment of illness severity for studies of natural history and intervention. The workshop also provided the opportunity to offer recommendations concerning future studies to develop and evaluate tests for biologic markers of CFS.

Field Experience Using the CDC Case Definition

To meet the case definition for CFS, a case must fulfill both major and minor criteria (2). The two major criteria are:

- A workshop was held 18 to 19 March 1991 at the National Institutes of Health to address critical issues in research concerning the chronic fatigue syndrome (CFS). Case definition, confounding diagnoses, and medical outcome assessment by laboratory and other means were considered from the perspectives of key medical specialties involved in CFS research. It was recommended that published Centers for Disease Control (CDC) case-definition criteria be modified to exclude fewer patients from analysis because of a history of psychiatric disorder.

Specific recommendations were made concerning the inclusion or exclusion of other major confounding diagnoses, and a standard panel of laboratory tests was specified for initial patient evaluation. The workshop emphasized the importance of recognizing other conditions that could explain the patient's symptoms and that may be treatable. It was viewed as essential for the investigator to screen for psychiatric disorder using a combination of self-report instruments followed by at least one structured interview to identify patients who should be excluded from studies or considered as a separate subgroup in data analysis. Because CFS is not a homogeneous abnormality and because there is no single pathogenic mechanism, research progress may depend upon delineation of these and other patient subgroups for separate data analysis.

Despite preliminary data, no physical finding or laboratory test was deemed confirmatory of the diagnosis of CFS. For assessment of clinical status, investigators must rely on the use of standardized instruments for patient self-reporting of fatigue, mood disturbance, functional status, sleep disorder, global well-being, and pain. Further research is needed to develop better instruments for quantifying these domains in patients with CFS.


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Table 1. Recommended Clarifications of Centers for Disease Control Research Case Definition for the Chronic Fatigue Syndrome

<table>
<thead>
<tr>
<th>Illness Category</th>
<th>Exclusions</th>
<th>Inclusions*</th>
<th>Recommended Tests†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic medical conditions</td>
<td>Major conditions to be considered in differential diagnoses are listed in reference 2 and include: malignancy, autoimmune disease, inflammatory disease, endocrine disease, neurologic disease, and chronic organic disease</td>
<td>Fibrnymyalgia‡</td>
<td>Tender-point examination‡</td>
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<td></td>
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<td>Optional or as clinically indicated:</td>
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<td>Serum cortisol, rheumatoid factor, and immunoglobulin levels</td>
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<td>Postinfectious disease</td>
<td>Chronic active hepatitis B or C; Lyme borreliosis, inadequately treated; HIV infection; tuberculosis</td>
<td>Infectious mononucleosis; adequately treated infection that is not typically associated with chronicity: toxoplasmosis, brucellosis, Lyme borreliosis§</td>
<td>Tuberculin skin test, Lyme serology in endemic area, HIV serology when indicated</td>
</tr>
<tr>
<td>Psychiatric and behavioral disorders</td>
<td>Psychoses: psychotic depression, bipolar disorder, schizophrenia</td>
<td>Nonpsychotic depression: concurrent, 1 month postonset or 6 months or more before onset: recurrent or nonrecurrent, somatoform disorders, anxiety disorders: generalized or panic disorder</td>
<td>Screen: General Health Questionnaire or combination of self-report instruments</td>
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<td></td>
<td>Substance abuse</td>
<td></td>
<td>For patients with positive screening results:</td>
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<td></td>
<td></td>
<td></td>
<td>Structured interview: Diagnostic Interview Schedule version III A or Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders. Third Edition Revised (DSM-III-R)</td>
</tr>
</tbody>
</table>

* Stratified by individual category in analysis.
† Tests are to be used in conjunction with complete detailed medical history and comprehensive physical examination (see Reference 2).
§ Recognized recrudescence and chronicity of active Borrelia infection was considered an exception.
\| Zung Self-rating Anxiety Scale, Symptom Checklist-90, Beck Depression Inventory.

1) new onset of persistent or relapsing, debilitating fatigue in a person without a previous history of such symptoms that does not resolve with bedrest and that is severe enough to reduce or impair average daily activity to less than 50% of the patient's premerid activity level for at least 6 months

2) fatigue that is not explained by the presence of other evident medical or psychiatric illness.

The minor criteria are:

- at least six symptoms plus at least two signs, or at least eight symptoms from the list below.

Symptoms:

- Mild fever or chills
- Sore throat
- Painful adenopathy (posterior or anterior, cervical or axillary)
- Generalized muscle weakness
- Myalgias
- Protracted generalized fatigue after previously tolerated levels of physical activity
- Generalized headaches
- Migratory arthralgia without swelling or redness
- Neuropsychologic complaints
- Sleep disturbance
- Main symptom complex developing over a few hours to a few days

Physical signs:

- Low-grade fever
- Nonexudative pharyngitis
- Palpable or tender anterior or posterior, cervical or axillary lymph nodes

Are the CDC Case-Definition Criteria Being Used and Uniformly Applied?

To determine how well the CDC case definition is working in the field, six CFS experts were asked to describe their study samples and procedures for diagnosis. Their reports were considered with respect to the following questions: Are the CDC case definition criteria being used and uniformly applied? Do ambiguities remain to be resolved? Do the case-definition criteria define a discrete group of patients?

Case ascertainment and diagnostic procedures described by these investigators indicated that current case-definition criteria are not being uniformly applied. Two investigators had discarded physical signs because they felt that they were too subjective, evanescent, or low in prevalence to be useful; and two had not eliminated all patients with a preexisting psychiatric disorder but had considered them separately in data analyses. Most of the investigators included as a separate category for data analysis those patients who had fewer than the required number of minor symptom criteria but...
who otherwise met the case definition. One has decided to no longer require a 50% reduction in daily activity as a defining characteristic because its estimation is problematic.

It appears that the CDC case definition is also not being used regularly in the general medical community. Of concern was the repeated observation that patients referred with a presumptive diagnosis of CFS often are found to have an existing psychiatric disorder or chronic disease that could explain their symptoms.

Do Ambiguities Exist in the Definition?

Some of the investigators remained uncertain whether all aspects of the first major criterion must be met, whether the caveat, “[fatigue] that does not resolve with bedrest” should be retained, and how reductions in activity in relation to premorbid levels were to be estimated.

It was unclear how the second major criterion—that fatigue not be explained by the presence of other medical or psychiatric illness—should be established without subjecting the patient to an unacceptable number of costly tests. Also, no consensus was reached on a method for handling the most troublesome confounding diagnoses such as fibromyalgia, Lyme disease, depression, and somatoform disorder.

Problems associated with defining minor criteria such as muscle weakness, neuropsychologic complaints, and sleep disturbance were noted, as were problems associated with the evanescent nature of physical signs.

Do the Criteria Define a Discrete Group of Patients?

The ability to define a discrete group of patients is a critical measure of the utility of a case definition. Study samples identified with a strict application of CDC criteria were demographically similar, typically had an infectious disease-associated onset, and showed no clustering by month of onset. Most patients were white women with a mean age between 30 and 40 years and resembled cases reported in other U.S. studies (1). It was reported that, in the ongoing CDC surveillance study, among patients who were excluded on the basis of history of psychiatric disorder but who otherwise met the case definition, stress was the primary associated feature at onset and that January was the most commonly cited month of onset.

Several investigators reported, however, that strict application of the psychiatric history exclusion criterion did not define a distinct group of patients on the basis of laboratory test results or physical measures. Moreover, cases that were excluded solely because of an insufficient number of symptoms also did not appear to differ in any respect from “true” cases. Some investigators voiced concern that the large number of symptoms required for case definition may bias the patient sample toward inclusion of persons with a somatoform or other psychiatric disorder (6, 7).

Case ascertainment methods may also introduce bias. The percentage of cases meeting the CDC definition varied from 25% to 66% in studies among patients who were self- or physician-referred to chronic fatigue clinics or CFS specialists. In the CDC surveillance study, referrals came from community physicians, and 66% of case patients had a history of an abrupt onset of infectious disease. In another study in which almost all referrals were from infectious disease specialists, 90% of case patients had an abrupt onset of infectious disease. As previously mentioned, most case patients in all these studies were women.

In an Australian study in which cases were ascertained from a random sample of community physicians to reduce referral and health-care-seeking biases, no difference was found in the prevalence of CFS between men and women (5). The case definition used in that study did not require the physical signs and symptoms listed in the CDC minor criteria. Thus, the relative effects of ascertainment compared with case definition on the ratio of women to men found in the study remains uncertain. The fact that 75% of Australian CFS patients reported a “viral” infectious disease onset and that the mean age at onset was 28.6 years (similar to findings in the United States) suggests that similar patients are being uncovered by each case definition.

Clarifications and Recommended Changes in Case Definition

Should the Case Definition Be Revised?

A major revision in the case definition was considered to be premature and beyond the scope of the workshop. Such a revision should be empirically derived and should be based on data accumulated in studies of large numbers of carefully documented patients. The CDC working definition has been enormously useful in providing a focus for CFS research and in promoting studies that are replicable.

One recommended modification was that patients with certain psychiatric disorders be included regardless of the time of symptom onset, provided that they otherwise meet the case definition (see Table 1). The working definition had been made deliberately restrictive to reduce heterogeneity among cases under study (8); however, it now seems prudent to make the definition less exclusionary. To ensure that studies are replicable and interpretable, such cases must be carefully delineated and their data handled separately in analyses. Study of well-characterized subgroups will foster an integrative approach that gives consideration to issues relating to comorbidity and possible common pathogenic pathways in patients with CFS and psychiatric stress. Such an approach should lead to a better understanding of factors underlying CFS (9).

The requirement that patients have a minimum number of symptoms and signs to meet the case definition for CFS is an item that may be considered for change based on data presented at the workshop and elsewhere. Because the CDC case definition was developed for research purposes and was not intended for rigid adherence by clinicians in private practice, certain specifications were arbitrarily chosen to promote reproducibility of study results (8).

Which Psychiatric Disorders Are Excluded and Which Are Included?

All workshop participants agreed that a history of any of the following psychiatric disorders excludes the di-
agnosis of CFS: schizophrenia, bipolar disorder, psychotic depression, and substance abuse.

The following disorders are included in the case definition but are identified clearly for separate analysis: major depressive episodes (not including those with psychotic features), panic disorder (with or without agoraphobia), generalized anxiety disorder, and somatiform disorder. These psychiatric disorders should be further distinguished by the timing of the onset of the disorder (for example, one discrete and self-limited episode well before the onset of chronic fatigue; chronic and recurring episodes well before the onset of chronic fatigue; active at the time of onset of chronic fatigue; clearly beginning after the onset of chronic fatigue) and by the response (if any) of the disorder to therapy (that is, does the psychiatric disorder improve, and do the chronic fatigue and associated somatic symptoms improve?). Confirmation of the date of onset from physician or medical records is advisable.

How Can Patients with Psychiatric Disorder Be Identified?

Several patient-administered, standardized screening instruments can help the clinician to identify those patients who may be suffering from a primary psychiatric disorder or who have a treatable disorder that is associated with chronic fatigue. The General Health Questionnaire was designed for this purpose (10), and combinations of instruments such as the Zung Self-rating Anxiety Scale, the Symptom Checklist-90, and the Beck Depression Inventory take little time to complete and have been found to be effective in identifying patients with chronic fatigue who are suffering from various forms of psychologic distress (11). Patients identified by these instruments can be referred for comprehensive psychiatric evaluation and, if necessary, for treatment.

It was felt to be essential for the researcher that at least one structured interview instrument, such as the Diagnostic Interview Schedule Version IIIA (DIS), based on the criteria for 16 psychiatric disorders in the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III), or the Structured Clinical Interview for DSM-III-R (SCID) be used before entry of a patient into a CFS study (12, 13). The former is used to determine a lifetime and current history of a psychiatric disorder and the latter to identify a current condition.

How Should Confounding Medical Disorders Be Handled?

Specific recommendations regarding patients with onset of CFS symptoms after an infection are given in Table 1. Patients with etiologically known, treatable infectious diseases that have resolved in terms of their acute clinical and laboratory features, but in whom fatigue and other subjective complaints persist despite appropriate therapy, and who otherwise meet CFS criteria can be included but should be stratified in the analysis. For example, patients with chronic debilitating fatigue that persists after a well-documented case of acute infectious mononucleosis, acute cytomegalovirus infection, or other viral infection would be included and considered in a separate subgroup analysis. Some disagreement arose as to whether a fatigue syndrome after properly treated early Lyme disease would qualify because of the known risk for true recrudescence and chronicity of active Borrelia infection; however, most workshop participants felt that such patients could be included. Well-documented, chronic active viral infections, such as chronic infection with hepatitis B virus, hepatitis C virus, or human immunodeficiency virus (HIV), should not be included in the case definition of CFS.

Many patients with fibromyalgia meet CDC criteria for CFS, and many with CFS meet CDC criteria for fibromyalgia (14, 15). Because fibromyalgia is also a descriptive diagnosis largely of exclusion, it was concluded that patients with unexplained musculoskeletal pain who meet the current American College of Rheumatology criteria should not be excluded if they otherwise meet CFS criteria; however, they should be stratified for separate analysis (16).

What Laboratory Tests Aid in the Diagnosis?

A main point of consensus was that no currently existing laboratory tests can be used to confirm the diagnosis of CFS. It was also agreed that, for clinical purposes, diagnostic testing in patients with suspected CFS should be done solely to exclude other diagnoses. An economical but comprehensive battery of laboratory tests, specified in Table 1, should be sufficient for this purpose when used in conjunction with a carefully obtained patient medical history and physical examination. In individual cases, clinical judgment will dictate whether additional tests are needed and with what frequency serial examinations should be conducted to detect the emergence of evidence to support an alternative diagnosis, such as multiple sclerosis.

The use of unproven “diagnostic” tools should be discouraged until CFS becomes better understood and until a laboratory test or battery of tests is shown by carefully controlled studies to be of value in establishing a diagnosis and clinical assessment. During the last decade, hopes have been raised by numerous reports of an increased prevalence in cases of a particular immunologic or virologic marker. Usefulness of these tests has been limited by study-to-study inconsistencies, lack of specificity, or prevalences too low to be useful for the individual patient. Newer findings hold promise but must await confirmation and further testing to assess their specificity, generalizability, and clinical utility (17-19).

In the Absence of Specific Tests for CFS, How Is Illness Severity Evaluated?

Ideally, both objective and subjective information would be collected to assess clinical status and disability; however, no laboratory test has been shown to be of proven value for this purpose, and few objective measures exist for fatigue, mood disturbance, functional status, sleep disorder, global well-being, and pain—the domains of interest in CFS. The clinician and investigator must rely on patient self-report instruments with
well-known reliabilities and validities used in as reproducible a way as possible. If new instruments are devised, they should be compared with established instruments for validity and reliability.

Measures selected should be sensitive to change in patient functional status. Patients with CFS often score so low on assessment scales that measures are not sensitive to modest change, thus causing “compression” artifacts. Some investigators have addressed this problem by extending the scale; however, the validity and reliability of such adjustments are unknown (20). Another strategy would be to have patients fill out two questionnaires, one reflecting status at its worst and the other reflecting current status.

One month appears to be the longest period for which patients can reliably recall events, thus the recommended frequency of assessment in therapeutic trials is once or more per month. In other kinds of studies with longer follow-up intervals, requested recall should be limited to 1 month.

In data analysis, the percentage change in the domain, not the mean change, is the most relevant and sensitive determinant. Change should be considered on an intrapersonal, rather than on a group basis. Broad subject-to-subject variability is common, and data typically are not normally distributed. Therefore, in most instances, nonparametric tests are required to assess the statistical significance of observed changes.

The problems associated specifically with measurement of fatigue were addressed in a previous workshop (21, 22). Few subjective scales are widely available; however, a fatigue score has been used for CFS assessment that was validated in patients with multiple sclerosis and in those with lupus (23). Both duration and severity should be assessed.

In measuring mood in other conditions, differences have been noted between results obtained using diagnostic instruments and results based on measures of symptomatology. It is advisable to use a combination of self-report and structured interview strategies.

Various forms of the Medical Outcome Survey (MOS) have been used to evaluate functional status; however, compression artifacts in patients with CFS were reported at the workshop. The use of measures, such as the MOS short form, that have previously been used in samples of patients with CFS could provide multiple studies with comparable data (24). The Sickness Impact Profile (SIP) is felt to be too difficult to complete and is not recommended for use in patients with CFS (25). With the possible exception of the use of an actimeter, a device for recording physical movement (26), no objective physical measure of disability exists, and physical examination findings are not currently considered particularly useful (22).

Sleep disturbance is often reported by patients with CFS. Preliminary data indicate that a questionnaire validated by formal studies in a sleep laboratory can be used to identify patients who have sleep disturbance (Buchwald D, Pascualy R, Bombardier C, Kith P. Personal communication). A sleep questionnaire could be useful in both the clinical and research settings.

A brief discussion of pain assessment was conducted. It was suggested that tender-point examinations be done using the method recommended by the American College of Rheumatology for the assessment of fibromyalgia (19).

Because the symptoms and complaints of patients with CFS are multidimensional, it was thought that a global well-being assessment instrument using a visual analog scale would be helpful.

How Can Development of Useful Laboratory Tests Be Expedited?

More scientific rigor is needed in the design, execution, and documentation of pilot studies. Working groups could be established to recommend specific methods, standardization procedures, and reagents. Recommendations were made that extend and amplify those concerning biologic marker evaluation made during a previous NIH-sponsored workshop (27-29). Immunologic tests received the most attention because markers, such as cytokine and natural killer-cell activities, are sensitive to both biologic factors and because laboratory testing conditions and reports concerning those markers have been the most inconsistent (30). Four major sources of variability were identified: patients, choice of comparison groups, specimen handling, and laboratory methods.

Patients

It was recommended that the duration and severity of the illness as well as symptom clusters be clearly described in addition to the method of ascertainment, the clinical definition used, and the way in which it was applied. Until the ways in which psychiatric disorders affect immunologic measures are better understood, it is preferable to study patients who have no preexisting or current psychiatric disorder. Because analgesics and antidepressant medications affect cytokine production, a prestudy washout period was recommended during which the patients would discontinue all medications (31-33). Appropriate counseling should be provided to patients from whom medication is withheld.

Comparison Groups

Comparison groups should be matched as closely as possible to the demographic features of the patient samples. Geographic matching is especially important in studies of agents that are purported to be etiologically associated. Whenever possible, concurrently collected control specimens should be used to control for the effects of seasonal factors and intercurrent infections.

Several types of control groups can be considered for inclusion in studies of CFS: patients with allergy (as many as 80% of CFS patients have IgE-mediated allergic disease) (34, 35); patients with well-defined psychiatric illnesses, such as affective disorder, similar to those seen commonly in patients with CFS; household contacts to control for environmental agents and exposures; and age- and sex-matched normal healthy controls from the same geographic area who have been screened for medical and psychiatric illness. The latter group serves as a general comparison group. Many argue that an ideal control group would comprise well but
sedentary individuals. The choice of control group(s) would depend on the particular study questions.

**Specimen Handling and Methods**

Patient and control specimens should be collected, transported, and preserved in a similar manner. Specimens should be coded to avoid observer bias, and matched specimens should be tested simultaneously using identical methods. It was felt that repeated testing of samples that were collected over a period of time from the same controls and patients would help to account for intrinsic variabilities. Whenever feasible, in planning sample collection procedures the investigator should consider diurnal and other cyclic variation (for example, menstrual cycle) especially for measures such as cytokine production that are sensitive to such biologic perturbations (36). If collection times cannot be synchronized, pertinent information should be recorded for consideration in interpreting results.

The issue of whether to use fresh or frozen patient material for tests of cell phenotypes and activities is problematic. The flow cytometric guidelines being developed by the AIDS Clinical Trials Group through the NIH currently recommend that fresh whole blood samples in ethylenediaminetetraacetic acid (EDTA), a chelating agent, be used and that samples be processed within a period of 6 hours so that an absolute total cell count can be obtained for the same sample that is used to determine the percentages of specific immunologic subsets (37). If frozen cells are used for functional assays, concurrently collected control specimens should be frozen along with patient specimens. Aliquots of frozen laboratory standards would be thawed and included with test samples as an internal control to maintain laboratory consistency.

**What Kinds of Research Are Needed To Advance Our Understanding of CFS?**

Because no convincing evidence exists as yet for a single pathogenic mechanism, it is appropriate that clinical and laboratory research on the etiology and pathogenesis of CFS continue to involve a broad range of potentially relevant areas including immunology, virology, neuroendocrinology, psychology, and psychiatry. Research is needed to develop better instruments for assessing clinical status and disability in patients with CFS. An integrated, multidisciplinary approach holds the greatest promise for meeting the challenge of CFS.

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