1999 NIH Funded CFS Research

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TITLE	ORTHOSTATIC INTOLERANCE IN CFS
P.I.	FREEMAN, ROY
GRANT NO.	5R01HL059459-02
Institution:	BETH ISRAEL DEACONESS MEDICAL CENTER

The over-all objectives of this proposal are: (1) to delineate the pathophysiology and pathogenesis of orthostatic intolerance in the chronic fatigue syndrome (CFS) (2) to investigate the role of orthostatic intolerance in producing the symptoms of CFS and (3) to use this information to apply physiologically appropriate therapeutic interventions and thereby decrease the symptoms of fatigue. The investigators plan to determine the physiological characteristics of orthostatic intolerance in CFS patients and healthy controls, characterize the differences in functional exercise capacity among CFS patients and between CFS patients and controls; and identify the relationships between the physiological measures of orthostatic intolerance, measures of functional exercise capacity, symptoms of orthostatic intolerance and symptoms of fatigue. Cardiovascular autonomic functions are to be assessed using standard tests of the sympathetic and parasympathetic nervous system; arterial baroreflex gain is to be measured using the heart rate and muscle sympathetic nerve activity response to pharmacological provocations; the cardiopulmonary baroreflex functions is to be assessed in response to graded central hypovolemia elicited by lower body negative pressure; plasma volume will be measured using the Evans Blue dye method; venous compliance assessed with venous occlusion plethysmography, Assessment of neurohumoral status and the functional exercise capacity is also to be included. These measures, which comprise the elements of orthostatic tolerance, will be compared with matched healthy controls. The relationships between these variables and the role of covariates such as the level of physical activity and psychiatric state, determined with standardized instruments, are to be analyzed using multivariate statistics.

TITLE	CIRCULATORY CONTROL IN YOUNG PEOPLE WITH CHRONIC FATIGUE
P.I.	SAUL, J P.
GRANT NO.	5R01HL062385-02
Institution:	MEDICAL UNIVERSITY OF SOUTH CAROLINA
There is no text on file for this abstract.	

TITLE	MUSCLE BLOOD FLOW AND CRONIC FATIGUESYNDROME
P.I.	MCCULLY, KEVIN K.
GRANT NO.	1R01HL065179-01
Institution:	UNIVERSITY OF GEORGIA
There is no text on file for this abstract.	

TITLE	MOTOR LEARNING IN CFS--NEURAL DYSFUNCTION IMPLICATION
P.I.	SERVATIUS, RICHARD J.
GRANT NO.	1R01NS038337-01A1
Institution:	UNIV OF MED/DENT NJ NEWARK

Chronic Fatigue Syndrome (CFS) patients have registered cognitive complaints such as impaired concentration, memory lapses, and confusion. These complaints are cited as the most debilitating aspect of their disorder. Our pilot study, funded through the New Jersey Chronic Fatigue Research Center, showed that acquisition of a new motor response is impaired in CFS patients. Failure to acquire the classically conditioned eyeblink response was associated with white matter abnormalities in the prefrontal cortex, which are more prevalent in CFS patients without a concurrent psychiatric diagnosis. The present proposal seeks to determine the nature and diagnostic specificity of the learning deficit, as well as advance our understanding of the pathophysiology of some of the cognitive complaints in CFS. We will compare acquisition of the classically conditioned eyeblink response in CFS patients without a concurrent diagnosis of depression to CFS patients with concurrent depression, depressed patients, and healthy sedentary controls. A two-tone discrimination procedure, wherein one tone (CS+) predicts the onset of the unconditioned stimulus (US) and one which does not (CS-), will be used. In this study, we will address two hypotheses derived from neuropsychological research, namely, that CFS patients without depression have slower information processing and they are also impaired in their ability to processes complex auditory information. To address the former, we will manipulate the time between CS+ onset and US onset, the interstimulus interval. To address the latter, we will reverse the contingencies between the CS+ and CS- with respect to the US. Learning of the eyeblink response will be related to performance on neuropsychological tests. We will also obtain MRI scans to quantify brain abnormalities. In this manner, we will relate the prevalence of brain abnormalities in CFS patients to learning and memory impairments. In the absence of a medical marker of the disorder, the diagnosis of CFS relies on concordance with the current case definition. The lack of a medical marker also hinders efforts toward an identification of the pathophysiology of CFS. Our strategy will be to employ a learning and memory paradigm about which a great deal is known concerning the underlying neuroanatomy, neurophysiology and neuropharmacology. We will then be in a position to relate learning abnormalities to brain pathology as measured in MRI scans and characterized by neuropsychological deficits.

NIAID

TITLE	Brain and Cardiovascular Studies
P.I.	NATELSON, BENJAMIN H.
GRANT NO.	2U01AI032247-090006
Institution:	UNIV OF MED/DENT NJ NEWARK
There is no text on file for this abstract.	

TITLE	Physiological Challenges in CFS
P.I.	LA MANCA, JOHN
GRANT NO.	2U01AI032247-090007
Institution:	UNIV OF MED/DENT NJ NEWARK
There is no text on file for this abstract.	

TITLE	Core--Patient Accrual and Data Analysis Facility
P.I.	NATELSON, BENJAMIN H.
GRANT NO.	2U01AI032247-099003
Institution:	UNIV OF MED/DENT NJ NEWARK
There is no text on file for this abstract.	

TITLE	MOTOR CONTROL IN CHRONIC FATIGUE SYNDROME
P.I.	STARR, ARNOLD
GRANT NO.	5R01AI034250-06
Institution:	UNIVERSITY OF CALIFORNIA IRVINE

Results from the prior grant period using electrophysiological recordings support the hypothesis that patients with CFS have a disorder of central motor control. Moreover, recent studies by others using transcranial magnetic stimulation also point to the central auditory pathway as being abnormal in CFS. The patients in our studies showed slowed reaction times in tasks requiring rapid responses and impaired brain activities accompanying motor response preparation. Transcranial magnetic stimulation has demonstrated a premature reduction of motor cortical output in CFS accompanying sustained motor activities. Our goals in the proposed new project are to define the time course of altered motor cortical function in CFS before and after a period of exercise-induced fatigue. The specificity of the abnormalities for CFS will be tested by comparison with a group of patients with clinical depression. The methods of study utilize neurophysiological recordings of slow brain potentials accompanying several different types of response preparation and transcranial magnetic stimulation of motor cortex to measure the extent of reduction of central motor drive.

TITLE	MECHANISMS OF IMMUNOLOGICALLY MEDIATED FATIGUE
P.I.	PETERSON, PHILIP K.
GRANT NO.	5R01AI035110-05
Institution:	MINNEAPOLIS MEDICAL RESEARCH FDN, INC.

Fatigue is a common clinical manifestation of infectious and autoimmune diseases; it is also the chief complaint of patients with chronic fatigue syndrome (CFS). Cytokines, which are produced during immune activation, have been hypothesized to affect brain cell function resulting in fatigue. The work proposed, which is potentially relevant to und erstanding CFS, will test the cytokine hypothesis of immunologically mediated chronic fatigue using recently developed murine models of whole cell Corynebacterium parvum antigen inoculation. The specific aims of this research proposal are to: (1) characterize a murine model of immunologically mediated chronic fatigue (Specific Aim 1); (2) evaluate the association between selected cytokine expression in splenic and brain tissues of mice and chronic fatigue development (Specific Aim 2); and (3) investigate the effects of drugs known to inhibit cytokine production on immunologically mediated chronic fatigue (Specific Aim 3). For these studies, fatigue will be quantified by measuring the degree and duration of reduction in spontaneous daily running activity on an exercise wheel following whole cell C. parvum antigen inoculation in C57BL/6 female mice. Serum cytokine levels (interleukin [IL]-1, IL-6, transforming growth factor-beta, interferon-alpha, and tumor necrosis factor-alpha) and cytokine mRNA expression in splenic and brain tissues of inoculated mice will be correlated with the development of chronic fatigue. Treatment of mice which display immunologically mediated chronic fatigue with drugs known to inhibit cytokine expression will be performed to assess their impact on development of chronic fatigue and their therapeutic potential in disorders involving immunologically mediated fatigue. These studies will enhance our understanding of the pathophysiology of immunologically mediated fatigue and will foster the development of new treatment strategies, particularly for patients with CFS.

TITLE	ESTIMATING RATES OF CFS IN A COMMUNITY SAMPLE
P.I.	JASON, LEONARD
GRANT NO.	5R01AI036295-05
Institution:	DE PAUL UNIVERSITY

Epidemiologic characterizations of the prevalence of Chronic Fatigue Syndrome are derived largely from data collected in treated populations, and these findings might be biased by differential access to health care treatment by gender, racial/ethnic and social class status. The goal of this study is to do a community-based prevalence study. the specific aims are: 1) to determine the rate of CFS in a socioeconomically and ethnically diverse sample 26,000 adults in Chicago; 2) to establish the relative prevalence of CFS across race/ethnicity, socioeconomic status and gender; and 3) to examine comorbidity between CFS and psychiatric disorders. It is hypothesized that the prevalence of CFS is higher than what has been found from clinically-based estimates. This study will be carried out in three stages. First, there will be an initial screening of a Chicago area sample. Respondents who meet CFS screening criteria will be followed up with a detailed structured psychiatric assessment. Stage three will involve a detailed medical history, physical exam, and laboratory tests. Univariate and multivariate statistical techniques will be utilized to delineate the overall rate of CFS in this Chicago population, its relative prevalence by gender, race/ethnicity, and social class, the prevalence of psychiatric comorbidity, and levels of functional impairment. Different definitions of CFS will be employed, and they will be compared and contrasted.

TITLE	DYSREGULATED 2-5A SYNTHETASE/RNASE L/PKR PATHWAYS IN CFS
P.I.	SUHADOLNIK, ROBERT J.
GRANT NO.	5R01AI038378-03
Institution:	TEMPLE UNIVERSITY

Research in the investigator's laboratory has focused on the two dsRNA-dependent IFN- inducible 2'5'oligoA synthetase/RNase L and PKR pathways. They have reported a statistically significant dysregulation in which the 2'5'A synthetase is present in its activated form, 2'5'A levels are elevated, RNase L is upregulated and the expression of PKR is downregulated. Recent data suggest additional differences unique to peripheral blood mononuclear cells (PBMC) from individuals with CFS compared to normal controls. Specifically, these findings in CFS PBMC are: 1) a 36kDa 2'5'A binding protein which is recognized by an RNase L polyclonal antibody; 2) a 90% decrease in cellular actin expression and 3) a pronounced change in total protein profiles. These data place the investigator in a unique position to explore the 2'5'A synthetase/RNase L and PKR systems in CFS. The proposed research will examine the 2'5'A synthetase and PKR pathways in an in vitro model and PBMC from a cohort of CFS patients and two control populations, in association with clinical symptomatology. The working hypothesis is that the characteristic signs and symptoms of CFS are associated with the dysregulation of the 2'5'A synthetase/RNase L and PKR pathways. The project will address: 1) the expression and activities of the four isoforms of 2'5'A synthetase; 2) the activators of 2'5'A synthetase; 3) the intracellular concentration, oligomer distribution and stability of 2'5'A; 4) the identification and characterization of the newly-discovered 36 kDa 2'5'A binding protein that is immunoreactive with RNase L antibody; 5) synthetic and natural routes for the inhibition of the upregulated RNase L in CFS; 6) the ultimate implications of the upregulated RNase L activity and 7) potential mechanisms for the decreased expression of PKR. The studies in the application are suggested to contribute to development of potential rational therapies for CFS.

TITLE	MONOZYGOTIC TWINS WITH CHRONIC FATIGUE SYNDROME--PREDISPOSITION OR PERCEPTION?
P.I.	BUCHWALD, DEDRA S.
GRANT NO.	2U19AI038429-050005
Institution:	UNIVERSITY OF WASHINGTON

CFS may be associated with the disruption of several physiological processes such as exercise capacity, sleep, cognition and immune function. Most investigations of CFS have used a case-control design with patients recruited from referral centers and controls often matched only of age and sex. Thus, these disorders have not adjusted for genetic and environmental influences. The study of monozygotic (MZ) twins discordant for CFS (i.e., one has CFS, one doesn't) adjusts for genetic variability and common familial exposures. We have constructed a large registry of twins in which at least one member has CFS or a similar illness. All Twin Registry members complete a comprehensive Registry Booklet and a structured psychiatric interview. Using this information and medical records, 21 pairs of CFS discordant twins (CFS-HY) have been selected for a 6-day evaluation that includes polysomnography, exercise capacity testing, neuropsychological assessment, SPECT imaging, a psychiatric and life events interview, tests of viral replication and the immune system (Phase 1). Data from the 17 CFS-HY twin pairs who have completed this evaluation demonstrate remarkably disrupted sleep, poor performance on the several cognitive tests and severely impaired exercise capacity in both twins, as well as intriguing differences in immune function and perceptual style. In Phase 2, the twins will return to Seattle 24-30 months after Phase 1 for further intensive study that will include polysomnography, neuropsychological testing, exercise capacity testing and measurement and measurement of immune function and perception. We will also examine 10 pairs of twins in which both members are health (HY-HY) to clarify the interpretation of the abnormalities documented in the healthy member of the CFS-HY pairs. Our aims are to confirm the Phase 1 results and to assess their stability and reproducibility; 2) improve the interpretation of Phase 1 abnormalities by expanded data collection using challenge studies and other approaches to bring out differences between the CFS-HY twins; 3) compare the results in the CFS-HY pairs with those obtained from HY- HY twins. If abnormalities are not found in HY-HY twins then the impairments in exercise, cognition and sleep may represent predisposing factors that place the healthy member of the CFS-HY pair at risk for illness; 4) establish the extent to which alterations in perception account for dysfunction in CFS.

TITLE	CORE--CLINICAL FACILITY
P.I.	BUCHWALD, DEDRA S.
GRANT NO.	2U19AI038429-059002
Institution:	UNIVERSITY OF WASHINGTON

The Clinical Core, will serve as a reservoir of well-characterized study subjects, both patients and controls, for behavioral, clinical and basic research studies. As such, the Clinical Core will serve as the source of patients for Chronic Fatigue Syndrome Clinical Research Center (CFS CRC). This Core has 4 major specific aims 1) to prospectively evaluate and follow a referral clinic-based cohort of patients with chronic fatigue and CFS; 2) to utilize this population as the basis for investigations on CFS; 3) to maintain databases and banks of biological specimens on a variety fatigued and control populations and to recruit new comparison groups to improve our understanding of CFS; and 4) to examine the operating characteristics of clinical evaluation instruments already collected and patient subgroups using available data. The results of a comprehensive evaluation, including information on demographic, medical, psychological, functional and social features on almost 1,200 patients seen in a referral clinic are currently in our data base. Ethnic/racial minorities comprise about 8% and women 77% of patients. Information on new patients is entered weekly and patients are re-evaluated periodically. Control groups available for comparison to CFS patients include healthy individuals and those with medical disorders post-mononucleosis fatigue, the symptom of fatigue but not CFS, major depression, multiple chemical sensitivities, rheumatoid arthritis, fibromyalgia and temporomanidubular joint disorder. Besides descriptive studies, other questions amenable to study using the Clinical Core include the development of a battery of appropriate assessment measures for use in CFS and the evaluation of diagnostic tests or objective markers. In fact, the use of the Clinical Core resources has resulted in the development of a promising test for CFS and in the submission of 5 R01 and many other grant applications.

TITLE	POPULATION BASED TWIN STUDY OF CHRONIC FATIGUE SYNDROME
P.I.	SULLIVAN, PATRICK F.
GRANT NO.	2U19AI038429-050006
Institution:	UNIVERSITY OF WASHINGTON

Despite considerable research, fundamental questions about CFS-like illness remain at best partially answered. These questions include its definition, validity, the degree to which it results from genetic versus environmental factors, and the nature of the substantial comorbidity observed with other conditions. The overarching aim of this Project is to shed light on a number of basic questions about CFS via a large population-based classical twin study. First, we will screen approximately 13,000 same-sex twin pairs who are members of the Mid-Atlantic Twin Registry for the lifetime presence of CFS-like illness (and several overlapping conditions such as fibromyalgia and major depression). Second, all twins who screen positive and a subset of twins who screen negative will be directly and blindly interviewed. The interviews will collect information about CFS symptoms, psychiatric disorders, stress life events, and medical history, and medical history. We will obtain additional standardized medical data via the subject's physician(s). Third, all screening, direct interview and medical data will be independently reviewed by three of the study investigators to determine the certainty than an individual meets criteria for "presumptive CFS" plus approximations of the Centers for Disease Control, British, and Australian CFS case definitions. Obtaining these unique data will allow us to address a set of critical questions regarding CFS-like illness. First, using the direct interview data will allow us to address a set of critical questions regarding CFS-like illness. First, using the direct interview data, we will use multivariate techniques to derive and empirical typology of prolonged fatigue and to assess how this typology compares to the major CFS case definitions to answer the question: "Is there a point of rarity that distinguishes the common symptom of fatigue from case definitions of CFS"? Next, we will quantify the role of genetic predisposition and environmental sources of variation from different definitions of CFS-like illness. This will allow us to address 2 important questions. Because the degree to which a complex and idiopathic condition is heritable is an important validator, we can address the question: "Do these definitions yield similar or different estimates of heritability?" In addition, examining the extent to which liability to CFS- like illness is due to additive genetic, shared environmental, and individual-specific environmental precipitating effects will yield glimpses into the fundamental nature of CFS. Finally, using multivariate twin analyses, we address the question: "To what extent to the genetic and environmental sources of variation of these other conditions overlap with CFS?"

TITLE	CHILDREN OF CHRONIC FATIGUE SYNDROME PATIENTS
P.I.	SMITH, MARK
GRANT NO.	2U19AI038429-050007
Institution:	UNIVERSITY OF WASHINGTON

The debilitating effects of CFS on the health of afflicted persons has been well-documented. This study broadens the scope of CFS research beyond the level of the individual to the family. Our primary purpose is to compare the fatigue study, functional performance and psychological health of children who have a parent with CFS with that of children of parents without CFS. A secondary goal is to examine the relationship between a parental CFS and a selected set of vulnerability markers in children. Perturbations in these indicators could serve as a mechanism for the inter-generational transmission of fatiguing illnesses. Probands will be married adult patients from the University of Washington Chronic Fatigue Clinic who meet diagnostic criteria for CFS and have at least one child between the ages of 10 and 17 living at home. The comparison group will be non-fatigued, married friends of CFS probands who are same sex and who have children in the same age range. All adults and children will be evaluated using a broad range of fatigue, functional performance, physical and mental health measures and selected vulnerability markers. These data will be used to address the following questions: Are children of CFS probands more likely to report high fatigue levels than children. of non-CFS probands? Are there differences in pain thresholds or cognitive functioning in the children of CFS probands? Are there higher rates of psychiatric disorders and psychosocial distress among children of CFS probands compared to children of non-CFS probands? Does having a parent with CFS impair the functioning of children and adolescents, or conversely, do the offspring of adults with CFS assume a disproportionate burden of responsibilities? For each of these questions the potential differential effects of age and sex of the proband and age, sex and pubertal status of the children will be investigated. This project elucidate several elements in our conceptual models for the pathophysiology of CFS. The examination of the effects on children of having a parent with CFS is focused on a familial predisposition to fatiguing illness. This predisposition may derive from the familial environment or genetics. Similarly, the targeted potentially pre-morbid perceptual may derive from the familial environment or genetics. Similarly, the targeted potentially pre-morbid perceptual vulnerability markers ask if there are subclinical alterations in the pain threshold and cognition of children of CFS parents; these children may be especially vulnerable for the development of fatiguing illnesses.

TITLE	CORE--BIOSTATISTICAL AND DATA MANAGEMENT
P.I.	ZEH, JUDITH
GRANT NO.	2U19AI038429-059001
Institution:	UNIVERSITY OF WASHINGTON

The Biostatistical and Data Management Core, will provide the statistical expertise and data entry and data management support needed by Chronic Fatigue Syndrome Clinical Research Center (CFS CRC) investigators. Its specific aims are to 1) provide consultation and collaboration on study design, methodology, and data analysis; 2) assist with the design of study forms and the evaluation of pre-testing and pilot data; 3) perform and supervise data entry; 4) maintain data bases and perform data management and quality control procedures; and 5) collaborate in the preparing and writing of manuscripts. The establishment of a Biostatistical and Data Management Core will allow new investigators to obtain valuable advice on CFS-related Projects, and established investigators involved in the CFS CRC to get advanced biostatistical consultation and evaluate novel approaches to research relevant to this CRC. A particular strength of this Core will be the availability of methodologists and analysts who have worked with the CFS CRC over the preceding 4 years, have gained extensive knowledge about the problems encountered in the classification of CFS and the appropriate biostatistical methods required to analyze complex data produced by this CFS CRC.

TITLE	MODEL FOR INDUCTION OF CFS
P.I.	JONES, JAMES F.
GRANT NO.	5R01AI040990-02
Institution:	NATIONAL JEWISH MEDICAL & RES CTR (CO)

The application was proceeded by an introduction that addressed critique from the first review. Changes and additions were bolded in this re-submitted application. Dr. Jones and colleagues at National Jewish Medical and Research Center in Denver, Colorado propose a case control study of adult patients (18-45 years) with CFS, half of whom have atopic disease compared to matched control groups. They plan to challenge with exercise and nasal allergy provocation 60 CFS patients and controls to determine if such provocation will evoke CFS symptoms as well as induce changes in inflammatory laboratory parameters. Their proposal would be used to define a model that would be usually for future pathophysiological studies and possible intervention trials for adults with CFS.

TITLE	AUTOANTIBODIES TO CELLULAR MATRIX ANTIGENS IN CFS
P.I.	TAN, ENG M.
GRANT NO.	5R01AI041033-03
Institution:	SCRIPPS RESEARCH INSTITUTE

On the basis of recent studies it has been shown that CFS sera contain antibodies to relatively insoluble cellular matrix antigens. Cellular structures (nuclear envelope, vimentin-containing intermediate filaments and a nuclear matrix particle visualized in immunofluorescence as reticulated speckles) associated with these antigens contain proteins that are part of the nuclear or cytoplasmic matrix. In collaboration with investigators at the University of Washington and at Harvard University, the PI and co-investigators at Scripps Research Institute will examine four research aims: 1) using previously collected blood samples from CFS patients from the two CFS center clinics and using currently developed assays the blood samples will be analyzed for the antibodies. They will be compared with patients with primary Sjogren's syndrome and primary fibromyalgia to determine whether differences in autoantibody specificities exist between different diseases and between CFS patients from different clinics; 2) ELISA assays will be developed for anti-lamin B1 and anti-vimentin using recombinant proteins expressed from cDNA clones, so that differences in antibody levels could be quantitated. This would be used in longitudinal studies of CFS patients to determine the role of humoral immunity in the natural history of the illness; 3) the possibility that there might be CFS-specific epitopes on lamin B1 and vimentin will be explored with expression products of PCR constructs, because if CFS-specific epitopes are detected, synthetic peptides of these regions could be used in highly specific immunological assays; 4) antibody screening of cDNA expression libraries will be performed to isolate the reticulated speckles nuclear antigen and a 45 kDa antigen. The antibody to the reticulated speckles could be a new or unique marker for CFS. The antibody to the 45 kDa antigen is present in Sjogren's syndrome but not in CFS-sicca and appears to be a distinguishing feature between the two clinical entities. Overall, these studies are aimed at rigorously defining autoantibody reactivities in CFS and may have etiologic implications.

TITLE	MECHANISMS OF RHINITIS IN CFS
P.I.	BARANIUK, JAMES N.
GRANT NO.	5R01AI042403-03
Institution:	GEORGETOWN UNIVERSITY

Rhinitis is present in 70% of CFS subjects. The investigators have intensively studied the nasal mucosa in CFS rhinitis to evaluate three hypotheses of CFS pathology: (1) immune dysfunction with atopy; (2) mucosal inflammation including viral infections; They propose to prospectively analyze atopy, mucosal inflammation, and neural dysfunction in age- and sex-matched CFS and control groups by using integrated nasal analysis models. They feel strongly that their hypothesis-driven approach will precisely define specific neural pathophysiological mechanisms in CFS, allow pharmacological manipulation of these dysfunctional systems, and potentially lead to the development of simple new diagnostic tests (i.e. nasal provocation) as the means to evaluate future treatments of CFS.

TITLE	COGNITIVE BEHAVIORAL STRESS MANAGEMENT INTERVENTION FOR CFS
P.I.	ANTONI, MICHAEL H.
GRANT NO.	1U01AI045940-010002
Institution:	UNIVERSITY OF MIAMI-MEDICAL

The proposed 5-year study examines the effects of a cognitive behavioral stress management (CBSM) intervention (including relaxation training and cognitive restructuring) on physical health status and illness burden in 150 (after attrition) patients diagnosed with Chronic Fatigue Syndrome (CFS). The study tests the efficacy of a conceptual model which holds that the interaction of psychological factors (distress and depression associated with either CFS related symptoms or other stressful life events) and immunologic dysfunction (elevations in cytokines such as tumor necrosis factor [TNF]-alpha and the macrophage activation marker, neopterin) contribute to: (a) the exacerbation of physical symptoms associated with CFS (e.g., fatigue, joint pain, fever) and subsequent increases in illness burden (operationalized as disruptions in daily activities due to fatigue and related physical symptoms); and (b) further dysfunction in the immune system (e.g., impaired lymphocyte proliferative responses to phytohemagglutinin [PHA] and natural killer cell cytotoxicity [NKCC]). The proposed revised study tests this model experimentally by first evaluating the effects of a 10 week group CBSM intervention upon the primary health outcome variables: physical health status (CFS symptoms), fatigue severity, CFS-related illness burden and functional quality of life. Secondly, this study examines the role of two sets of hypothesized mediator variables: (l) reductions in psychological distress and depression levels; and (2) immune system modulation (less impaired NKCC and PHA responsivity, lowered TNF-alpha peptides and TNF-type II receptors in serum, reduced neopterin levels, reduced numbers of lymphocyte subsets expressing activation markers). To bring about these effects the intervention is hypothesized to directly modulate a set of psychosocial intervention targets that we hypothesize will influence the mediator variables. These intervention targets include reductions in distorted cognitive appraisals, greater use of active and engaging coping strategies, increased coping self-efficacy and increased perceptions of social support provisions. This is a randomized experiment with a 12-week CBSM (plus education and standard care) condition vs. an Education plus standard care (ED/SC) control condition, At the end of the 12-week CBSM intervention, the experimental group will continue on a standard of care regimen and will be monitored for their adherence to the techniques learned in the CBSM intervention and for intercurrent medical treatment. At the end of the 12-week ED/SC period the control group will be subsequently monitored as they continue on their standard of care. We will follow subjects at 6 and 12 months post-CBSM to assess treatment carryover and to correlate prospectively pre-post CBSM changes in mediator and health outcome variables measured at these follow-up points.

TITLE	EFFECT OF STRESS AND CBSM ON NATURAL KILLER CELL ACTIVITY IN CFS
P.I.	FLETCHER, MARY A.
GRANT NO.	1U01AI045940-010004
Institution:	UNIVERSITY OF MIAMI-MEDICAL

Natural cell mediated immunity is frequently decreased in individuals who meet the case definition of chronic fatigue syndrome (CFS). Our research group and others have noted that exposures of healthy individuals as well as immunocompromised persons to acute and chronic stressors have an adverse effect on natural killer (NK) cell function, and that this adverse stress effect is susceptible to amelioration by behavioral interventions in which cognitive restructuring and relaxation training are taught. In this Multidisciplinary Research Center, Project 2 will carry out such an intervention for individuals who meet the diagnosis criteria for CFS. The intervention will be carried out over a 12 week period. Blood samples from both pre-intervention and post-intervention will be available for study in Project 4. Also available will be 2 samples collected 12 weeks apart on CFS subjects who do not receive the intervention, but are in an education/control condition. The Administrative Core will enroll healthy, sedentary controls for both Project l and Project 4 and for the Laboratory Core as normal subjects for all assays being done. The proposed Center will provide a mechanism to advance our understanding of NK cells and CFS. A detailed comparison will be made of markers of NK cell cytotoxic capacity as well as actual killing of tumor cell target cells. The differences between effect of the intervention on NK cell function can be evaluated. In addition to the traditional chromium release cytotoxicity assay, Project 4 will look at important markers of NK cell functional status not yet evaluated in CFS. These will include flow cytometric determination of intracellular perforin and determination of degree of expression on NK cells of the surface membrane adhesion molecules, L-selectin (CD62L), LFA-1 (CDlla) and CD56 by fluorescence intensity measurements. These substances are associated with the ability of NK cells to-kill target cells and/or to interact with vascular epithelial cells and pass from peripheral circulation into tissue. The relationship of these markers to the low NK cell activity associated with CFS, to effects of acute and chronic stress on NK cell function or to the modulation of life stress by behavioral interventions has not previously been studied. We will examine the effects on NK cell cytotoxicity, intracellular perforin levels and surface markers of in vitro exposure of peripheral blood cells to stress hormones (epinephrine, norepinephrine, cortisol) and tumor necrosis factor-o:. All of these studies will be done pre/post intervention in the 2 CFS groups of subjects and one time in the healthy, sedentary controls. This design will allow the determination of differences between CFS and healthy controls as well as the impact of the behavioral intervention by comparing findings before and following the intervention relative to CFS control subjects.

TITLE	CORE--LABORATORY FACILITY
P.I.	FLETCHER, MARY A.
GRANT NO.	1U01AI045940-019003
Institution:	UNIVERSITY OF MIAMI-MEDICAL

The LABORATORY CORE will provide the assessments of soluble mediators, lymphocyte surface markers, hematological parameters and lymphocyte function in support of the scientific agenda of this Center. For the intervention study, Project l, measurements of plasma and inducible tumor necrosis factor-alpha: (TNF-alpha:), soluble tumor necrosis factor receptor type II (sTNFII), interleukin-1-alpha (IL-1alpha), and IL-6, adrenocorticotropic hormone (ACTH) cortisol, norepinepherine (NE), epinephrine (E), erythropoitin, renin, reticulocytes, red blood cell (RBC) indices and electrolytes will be made at the time points defined in the experimental design for this studies. For Project 3, selected subjects from Project 1 will undergo a laboratory study of hemodynamics and autonomic mechanisms both pre- and post- intervention and serial measurements of plasma catecholamines will be made. For the Cognitive Behavioral Stress Management (CBSM) intervention study, Project 2, the following immunology assays will be done on the serial samples collected on subjects at T0, Tl, T2 and T3 as stipulated in the study design for that project: lymphocyte proliferation assays (LPA) and inducible cytokines in response to the mitogen, phytohemagglutinin (PHA); natural killer cell cytotoxicity (NKCC) against the tumor cell target, K562; number and percent of CD4, CD8 and activated sunsets of these, and NK cells (CD56+CD3-) using 4 color flow cytometry; plasma levels of neopterin, TNF-alpha and sTNFRII. Project 4 will study NK cells in a subset of subjects from Project 2 and will make use of the NKCC data done for that protocol. The Administrative Core will recruit 50 healthy sedentary controls. Blood samples from these controls will be assessed for all of the variables determined in this core, at a rate of 10 controls per year.

TITLE	VENOUS DYSFUNCTION IN CHRONIC FATIGUE SYNDROME
P.I.	STEWART, JULIAN M.
GRANT NO.	1R03AI045954-01
Institution:	NEW YORK MEDICAL COLLEGE
There is no text on file for this abstract.	

TITLE	SIBERIAN GINSENG FOR THE TREATMENT OF CHRONIC FATIGUE
P.I.	HARTZ, ARTHUR J.
GRANT NO.	1R03AI045982-01
Institution:	UNIVERSITY OF IOWA
There is no text on file for this abstract.	

TITLE	FLUDROCORTISONE FOR INDIVIDUALS WITH CHRONIC FATIGUE SYNDROME AND HYPOTENSION
P.I.	STRAUS, STEPHEN E.
GRANT NO.	1Z01AI000812-03
Institution:	

Chronic fatigue syndrome (CFS) is a serious health problem in the United States, affecting at least 3 of every 1,000 patients seen in general medicine clinics. It is estimated that the prevalence rate in the United States is as much as 100/100,000 persons. No effective treatment has been identified. Recent observations suggest a strong association between CFS and a treatable disorder in the regulation of blood pressure known as neurally-mediated hypotension (NMH). In a small unblinded studies, treatment with fludrocortisone and other medications directed against NMH has appeared to be beneficial, with 40% of treated patients reporting an almost complete resolution of symptoms and another 30% reporting some improvement. The specific aim of this randomized double blind, placebo-controlled trial is to determine whether fludrocortisone is efficacious for those with CFS. In this study, we randomized 100 adults with CFS and NMH, as defined by abnormal responses to tilting, to receive either fludrocortisone or placebo. The participants completed self-assessment forms on mood, energy, activity, and performance. The primary indicator of efficacy is a 15-point improvement (on a scale of 1 to 100) in the general sense of well being score. All subjects were 18-49 years of age who satisfy the 1994 CDC criteria for CFS, had undergone a medical evaluation to exclude other causes of CFS, and had hypotension provoked during stage 1 or 2 of an upright tilt table test. Together with our collaborators at Johns Hopkins, we have screened nearly 180 subjects, finding about 60% of them to be abnormal. All subjects have been enrolled. The blinded treatment has been well tolerated with no serious adverse reactions, nor concerns of our Data and Safety Monitoring Board. The study data are now being analyzed and should be available for reporting by late summer, 1999. - Randomized controlled trial, chronic fatigue syndrome, neurally-mediated hypotension - Human Subjects

NIAMS

TITLE	HPA AXIS DYSREGULATION IN FIBROMYALGIA
P.I.	CROFFORD, LESLIE J.
GRANT NO.	3M01RR000042-39S11009
Institution:	UNIVERSITY OF MICHIGAN AT ANN ARBOR

Patients with Fibromyalgia (FM) and Chronic Fatigue Syndrome (CFS) display disturbances in hypothalamic-pituitary-adrenal (HPA) axis function that suggest failure of central regulatory mechanisms. We will characterize the basal, spontaneous secretory characteristics and stimulated activity of the HPA axis in patients with FM and CFS, compared to a matched population of healthy volunteers.

NIMH

TITLE	AUDITORY WORKING MEMORY IN CFS--AN FMRI STUDY
P.I.	LANGE, GUDRUN
GRANT NO.	1R01MH057272-01A1
Institution:	UNIV OF MED/DENT NJ NEWARK

There is no text on file for this abstract

TITLE	RESEARCH CENTER ON THE PSYCHOBIOLOGY OF ETHNICITY
P.I.	LIN, KEH-MING
GRANT NO.	5R01MH047193-10
Institution:	HARBOR-UCLA RESEARCH & EDUC INST

The Center was established in 1990. Its primary mission is to bridge the gap between biological and sociocultural research efforts and to contribute towards the establishment of a more fully integrated bio-psycho-socio-cultural approach to psychiatric research and practice. This renewal application seeks five years of support to continue and expand the Center's research agenda. Building upon the solid foundation of its infrastructure and research tools developed over the past five years, the Center plans to apply advanced research methodologies into clinical and community settings, to concurrently assess the influence of biological, psychosocial and cultural factors in psychiatric morbidity, nosology and treatment responses, and to examine how these factors might interact with one another. Also introduced will be health services methodology to allow the use of data derived from an existing medication prescription monitoring system. The research projects included in this proposal include five research areas examining the following issues: (1) the clinical utility of recently developed pharmacogenetic probes with multi-ethnic/multi-cultural patients suffering from different psychiatric conditions; (2) the use of MR spectroscopy to measure lithium concentration in the brain in relation to ethnic differences in response to lithium; (3) biopsychosocial assessment of major depression, both cross-sectional and longitudinal, in a multi-ethnic mental health care setting; (4) long- term longitudinal follow-up of a community sample of Chinese-American patients with ICD-10 defined neurasthenia; and (5) the use of a large secondary data set of medication prescriptions to study how ethnicity interacts with other clinical and sociodemographic variables in affecting the patterns of medication prescription. This fuller integration of biomedical and sociocultural traditions will help to ensure that advances in psychiatric research will be appropriately and effectively applied to patients from diverse sociocultural and ethnic backgrounds. At the same time, cross-ethnic and cross-cultural observations and testing will contribute significantly to the validation and further development of psychiatric theories and practices.

TITLE	THE NEUROBIOLOGY OF MAJOR DEPRESSION
P.I.	GOLD, PHILIP W.
GRANT NO.	1Z01MH002659-07
Institution:	

*We study the neurobiology of major **depression**. The fundamental central nervous system pathophysiological changes that underlie the core affective and cognitive symptoms of major **depression** also play a role in the fact that patients with major **depression** have twice the expected death rate at any age, independent of suicide. In addition, patients with major **depression** show a marked increase in the incidence of premature ischemic heart disease and osteoporosis. Our work consists of designing and performing studies to elucidate fundamental central nervous system mechanisms that contribute both to the affective and cognitive symptoms of major **depression** as well as their long-term medical consequences. As a corollary, our goal is to develop improved means for the diagnosis, treatment,, and prevention of the psychological and medical components of depressive disorders. Our clinical studies proceed predominantly in a group of 100 families studied longitudinally at the NIH for over twenty years. In 60 families the mother entered the study with a diagnosis of major **depression** and two children between the ages of 2 and 4. This population represents an ideal group for prospective studies in the years to come. In the past year, we have begun to elucidate the pathophysiology of the significant loss of bone mineral density we first described in patients with major **depression** via biospy of the anterior iliac crest. To date, we note decreased bone turnover and a marked decrease in the bone mineralization rate. We have also found that patients with major **depression** (matched closely with volunteers with respect to height, weight, and gender) show a significant decrement in lean body mass that correlates with bone mineral density. We have also found that patients with melancholic **depression** show profound, around-the-clock increases in CSF NE levels, that NE and the hypercortisolism mutually reinforce one another, and that these defects are closely related to defects in specific components of the central CRH system. We have developed and deployed a non-peptide CRH type 1 receptor antagonist. Utilizing this compound, we have demonstrated that CRHplays a tonic role in the behavioral, autonomic, metabolic, and endocrine responses to stress in rhesus macaques. These studies are premonitory to introducing this compound for study in human subjects. - atypical **depression**, melancholic **depression**, pathophysiology, osteoprosis, ischemic heart disease, CRH, norepinephrine - Human Subjects*

NCRR

TITLE	EVALUATION OF MUSCLE FUNCTION IN PERSIAN GULF VETERANS
P.I.	VANDENBORNE, KRISTA K.
GRANT NO.	5M01RR000040-390711
Institution:	UNIVERSITY OF PENNSYLVANIA

The major objective of this proposal is to investigate the etiology responsible for the ongoing chronic fatigue and muscle weakness in veterans with the Persian Gulf illness. For this purpose we will evaluate skeletal muscle function of Persian Gulf Veterans with severe chronic fatigue and Persian Gulf veterans who were deployed but who have no medical problems. We hypothesize muscle function is impaired in Persian Gulf veterans with a symptom profile consistent with CFS. In addition, we hypothesize that the severity of chronic fatigue in this population is related to the degree of muscle dysfunctioning. To test these hypotheses a battery of tests will be performed on Persian Gulf veterans with severe chronic fatigue and on control veterans with no medical complaints. These measurements will include 31P-Magnetic Resonance spectroscopy (MRS), Magnetic Electrodiagnostic evaluation of motor unit recruitment, Muscle enzyme assays, Isokinetic and Isometric testing, and Functional Status Questionnaire. Complementary to the functional tests, the subjects will be screened for AMP deaminase (AMPD) deficiency.

TITLE	MUSCLE BLOOD FLOW AND CRONIC FATIGUESYNDROME
P.I.	MCCULLY, KEVIN K.
GRANT NO.	1R01HL065179-01
Institution:	UNIVERSITY OF GEORGIA

There is no text on file for this abstract.

TITLE	MITOCHONDRIA IN CHRONIC FATIGUE SYNDROME PATHOPHYSIOLOGY
P.I.	CHAZOTTE, BRAD J.
GRANT NO.	3M01RR000046-39S21069
Institution:	UNIVERSITY OF NORTH CAROLINA CHAPEL HILL

The purpose of this study is to determine if mitochondrial bioenergetic function is impaired in the cells of Chronic Fatigue Syndrome (CFS) patients compared to normal, healthy individuals.

TITLE	MODEL FOR INDUCTION OF CHRONIC FATIGUE STUDY
P.I.	JONES, JIM
GRANT NO.	5M01RR000051-381090
Institution:	UNIVERSITY OF COLORADO HLTH SCIENCES CTR

The mechanisms underlying the clinical syndrome known as CS are unkown. We and others have suggested that CFS onset and symptoms are frequently associated with infection and inflammation, including atopy as a specific type of inflammation. Patients often relate exacerbations of their illness following tiring physical activity and allergen exposure. Recent studies have suggested a link between exercise and release of cytokines and complement activation possibly as a consequence of muscle injury induced by the activity. This trigger of the syndrome is universal and its importance led to its inclusion in the 94 revision of the working definition. Triggering by exposure to a single allergen is often a patient complains, as is exacerbation of the symptoms during allergen season. This study will evaluate the role of these "triggers" in the exacerbation of this chornic illness state with the eventual goal of defining the abnormal responses which induced and perpetuate the development of CFS. Year I of this grant was designed to enroll 40 subjects, 20 of whom with CFS and 20 control subjects with 1/2 (10) in each group being allergic. As of November 30, 1998 40 individuals have been enrolled. Since the critical numbers will be acquired at the end of year 3, future enrollment will concentrate on achieving a 3:1 ratio of female to males in such group and age matches within 5 years. Recruitment is an ongoing process with a goal of 50 indivudals during year 2. The grant is still in the data gathering stage, no findings are available. Based on the study design of collecting data over a 3 year period, analysis of challenges are not expected to show meaningful results until the end of that time. Analsysis for trends will be performed during the second year, even though the numbers of subjects in each of the groups may be too small to expect definitive differences. The specific aims described in the original application remains in effect. On additional parameter includes obtaining a blood specimen before challenges for mononuclear cell RNA to be analyzed for cytokine mRNA expression using a microarray technique at the CDC as part of the ongoing CFS project at that institution. Subjects are asked to join this project as an add-on to our grant.

TITLE	EXERCISE INTOLERANCE IN CHRONIC FATIGUE SYNDROME
P.I.	SIETSEMA, KATHY E.
GRANT NO.	5M01RR000425-300573
Institution:	HARBOR-UCLA RESEARCH & EDUC INST

To characterize acute cardiorespiratory responses to exercise in patients with CFS and correlate these responses to patient's clinical features and activity patterns; to determine muscular work efficiency in CFS; to determine the physiologic effect of preconditioning with an exercise stress on subsequent cardio-respiratory and muscular responses to exercise and to determine if performance of exercise stimulates an acute phase response in patients with Chronic Fatigue Syndrome

TITLE	MECHANISMS OF RHINITIS IN CFS
P.I.	BARANIUK, JAMES N.
GRANT NO.	5R01AI042403-03
Institution:	GEORGETOWN UNIVERSITY

Rhinitis is present in 70% of CFS subjects. The investigators have intensively studied the nasal mucosa in CFS rhinitis to evaluate three hypotheses of CFS pathology: (1) immune dysfunction with atopy; (2) mucosal inflammation including viral infections; They propose to prospectively analyze atopy, mucosal inflammation, and neural dysfunction in age- and sex-matched CFS and control groups by using integrated nasal analysis models. They feel strongly that their hypothesis-driven approach will precisely define specific neural pathophysiological mechanisms in CFS, allow pharmacological manipulation of these dysfunctional systems, and potentially lead to the development of simple new diagnostic tests (i.e. nasal provocation) as the means to evaluate future treatments of CFS.