2001 NIH Funded CFS Research
NHLBI

TITLE	Circulatory Dysfunction in Chronic Fatigue Syndrome
P.I.	STEWART, JULIAN M.
GRANT NO.	1R01HL066007-01A1
Institution:	NEW YORK MEDICAL COLLEGE

Chronic fatigue syndrome (CFS) is associated with orthostatic intolerance which often takes the form of postural orthostatic tachycardia syndrome (POTS) in adolescents. Preliminary data suggest the novel concept that defective vasoconstriction produces POTS in CFS with cardiac autonomic changes as a secondary response. CFS patients will be compared to healthy controls and to controls with simple faints to test 3 hypotheses: 1) Blood is redistributed peripherally and redistribution is enhanced during orthostasis producing increased microvascular filtration and dependent edema. Central hypovolemia causes decreased cardiac output, reflex tachycardia and reduced cerebral blood flow. This is enhanced during orthostasis producing increased microvascular filtration, dependent edema, and peripheral pooling. These changes alter the interstitium, and cause reflex tachycardia, reduced cerebral blood flow and often hypotension. Blood volume and cardiac output using the indocyanine green dye dilution technique will be measured supine, during conventional 700 head-up tilt, and during low angle head-up tilt. Cerebral blood flow velocity (CBFv) will be estimated by transcranial Doppler ultrasonography. Thoracic, splanchnic, and pelvic vascular volumes will be measured by impedance plethysmography, and limb blood flow, arterial flow, venous volume-pressure relation, and venous pressure will be measured by venous occlusion strain gauge plethysmography. These will show increased blood flow to lower extremities when upright. Central hypovolemia will occur and will reduce CBF and produce symptoms of CFS. Cardiac autonomic status including baroreflex will be assessed by heart rate and blood pressure variability and transfer function. Baroreflex and heart rate variability will be decreased and blood pressure variability will be increased related to circulatory deficit 2) The defect in vasoconstriction is heterogeneous comprising abnormal arterial baroreflex mediated sympathetic vasoconstriction in one subgroup of CFS patients and abnormal local vasoconstriction in a second subgroup with defective veno-arteriolar reflex (arterial baroreflex insensitive dysfunction). Low angle tilt will be used to activate baroreflex mediated and local reflexes. Local reflexes including myogenic, metabolic and veno-arteriolar will be sorted out through use of supine testing designed to specifically stimulate a specific reflex (limb hang, large pressure step and reactive hyperemia) and measuring peripheral resistance. 3) Cardiac autonomic findings are secondary to circulatory changes. Thus, tachycardia relates to vagal withdrawal because of circulatory insufficiency. CFS patients will be treated with midodrine or placebo in a cross-over study. Using supine and low angle tilt experiments, circulatory measurements and psychological instruments will be combined to demonstrate that circulatory abnormalities, autonomic abnormalities and symptoms correct in a subgroup of CFS patients with low resting peripheral resistance.

TITLE	ORTHOSTATIC INTOLERANCE IN CFS
P.I.	FREEMAN, ROY
GRANT NO.	5R01HL059459-04
Institution:	BETH ISRAEL DEACONESS MEDICAL CENTER, MA

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	MUSCLE BLOOD FLOW AND CFS
P.I.	MCCULLY, KEVIN K.
GRANT NO.	5R01HL065179-04
Institution:	UNIVERSITY OF GEORGIA

This abstract is not available.

TITLE	RBC MASS, ANS INTEGRITY & SYNCOPE SUSCEPTIBILITY IN CFS
P.I.	HURWITZ, BARRY E.
GRANT NO.	5R01HL065668-02
Institution:	UNIVERSITY OF MIAMI-MEDICAL

The pathogenesis of the chronic fatigue syndrome (CFS) includes severe and debilitating fatigue, orthostatic intolerance, and the disruption of hematological, autonomic, and cardiovascular function. Our preliminary findings suggest that: 1) reduced red blood cell (RBC) mass is a critical hematological marker of CFS; and 2) RBC mass expansion improves orthostatic tolerance and fatigue beyond that ascribed to plasma volume expansion alone. However, the physiologic mechanisms underlying the RBC mass treatment effect and the relationship of such mechanisms to individual differences in treatment response have not been elucidated. This proposed 5-year study will screen 150 CDC-defined CFS men and women and classify them into low and normal RBC mass groups. The CFS subjects (90 of 105 enrolled) will be studied before and after a 3-month intervention in a randomized double-blind, placebo-controlled study of pharmacotherapy to expand RBC mass; specifically, two CFS groups with low RBC (RBC-treated and placebo-treated) will be compared to another CFS group with normal RBC mass (standard and usual care). To assess whether the diminished cardiac function, characteristic of CFS orthostatic intolerance, is a consequence of myocardial origin, echocardiographic evaluation of left ventricular structure and function (left ventricular mass and wall thickness, compliance, and contractility) will be performed. In addition, autonomic integrity will be assessed during a standardized battery of tests (supine rest, paced respiration, Valsalva maneuver, lying-to standing, and sustained handgrip); baroreceptor sensitivity and alpha- and beta-adrenoceptor sensitivity will he tested using adrenoceptor pharmacologic challenge (phenylephrine, isoproterenol). To determine orthostatic susceptibility, a 70 head-up tilt (HUT) test combined with beta-adrenoceptor infusion at 2 mug/min (and then again at 5 mug/min, if the previous HUT failed to induce orthostatic hypotension) will be performed. We will further examine the treatment effect on exertional fatigue and hemodynamic and autonomic physiologic response to the HUT tests. Finally, the relation between the criterion (orthostatic hypotension susceptibility) and the predictors (hemodynamic, autonomic, cardiac structure/function and baroreceptor, alpha-adrenoceptor and beta-adrenoceptor sensitivities) will be evaluated to determine the extent to which the predictors are mediating the treatment effects on orthostatic hypotension susceptibility.

NINDR

TITLE	COMPREHENSIVE CENTER FOR INFLAMMATORY DISORDERS
P.I.	FLOOD, PATRICK M.
GRANT NO.	5P60DE013079-03
Institution:	UNIVERSITY OF NORTH CAROLINA CHAPEL HILL

Chronic inflammatory disorders are one of the biggest health problems in America today. This application describes the Comprehensive Center for Inflammatory Disorders whose mission is to support the identification and implementation of the full range of discovery from research on the basic mechanisms of inflammation to improved methods in the prevention and treatment of oral and systemic inflammatory diseases and disorders. The goals of the Center are to: 1) integrate studies on the fundamental mechanisms of cellular responses to inflammatory stimuli to better understand the basis of cellular activation, motility, and function that occur during inflammatory responses; 2) integrate basic research studies on inflammation with animal, patient-based and population research to better understand the cellular and molecular basis of oral inflammatory disorders; 3) identify several new and innovative approaches to the prevention, diagnosis, and treatment of chronic inflammation and facilitate their development into effective interventions for the treatment of oral and systemic inflammatory diseases and disorders within 5 years; 4) utilize and expand ongoing research on community education, screening, counseling, and related service programs to find better ways to expand public implementation of new advances in the prevention, diagnosis, and treatment of chronic oral and systemic inflammatory diseases and disorders; 5) integrate discovery from laboratory, clinical, population, education or community-based research into ongoing Center activities or new Center initiatives; and 6) promote programs for the education of health professionals and the public on the etiology, prevention, diagnosis, and treatment of chronic inflammatory diseases and disorders. The Center consists of 4 workgroups in the areas of fundamental, clinical, epidemiologic, and community outreach and outcomes research which are supported by an administrative, educational, technology transfer, and research support core. This Center core is designed to: 1) stimulate sharing, mutual interpretation, and integration of information on inflammation or inflammatory disorders obtained through research discovery; 2) provide mechanisms that allow the rapid development of discovery into new research projects, therapies, interventions, or potentially marketable products; 3) educate health professionals and the public on health issues of oral and systemic inflammatory disorders; and 4) make available to each product essential administrative support, research facilities, research services, coordination, and scientific leadership.

NINDS

TITLE	Pathophysiology of Neuroimmune Communication
P.I.	QUAN, NING
GRANT NO.	1R01NS040098-01A2
Institution:	OHIO STATE UNIVERSITY

Two neuroimmune communication pathways, the ascending vagus nerve and cells of the blood-brain barrier, have recently been identified to relay signals of peripheral infection to the brain by inducing the expression of IL-1 and TNF-alpha in the central nervous system (CNS). Chronic expression of IL-1 and TNF-alpha in the CNS, however, has been shown to contribute to the pathogenesis of many CNS diseases including chronic fatigue syndrome, AIDS dementia, and various neurodegenerative diseases. Whether chronic peripheral infection can cause CNS diseases by driving chronic production of IL-1 and TNF-alpha in the brain has not been studied. In a recently created infectious disease model, striking patterns of neuropathological changes were found in the brain without infiltration of either the pathogen or peripheral inflammatory cells into the brain parenchyma. The neuropathological changes were closely associated with the chronic expression of IL-1 and TNF-alpha in the brain. These pathological changes was enhanced by blocking the inhibitory mechanisms for IL-1 and TNF-alpha expression and reduced by intracerebral administration of specific antagonists of IL-1 and TNF-alpha. Therefore, it is hypothesized that induction of IL-1 and TNF-alpha in the brain by chronic peripheral infection is a mechanism for the pathogenesis of CNS diseases. Using this infectious disease model, the following specific aims are proposed to test this hypothesis: 1) Determine and characterize the neurotoxic effects mediated by chronic CNS production of IL-1 and/or TNF-alpha; and 2) Determine the role of glucocorticoids and prostaglandins in regulating the chronic expression of IL-1 and TNF-alpha in the brain. Specific Aim 1 is designed to characterize the neurotoxic effects attributable to the chronic expression of IL-1 and/or TNF-alpha in the brain induced by neuroimmune activation. In Aim 2, whether glucocorticoids and prostaglandins importantly controls the levels of chronic expression IL-1 and TNF-alpha and the manifestation of related neurotoxic effects in the brain will be determined. Glucocorticoids and prostaglandins are the two major feedback inhibitory regulators for IL-1 and TNF-alpha expression. Finally, the use of anti-inflammatory drugs in modulating the neurotoxic effects of chronic CNS production of IL-1 and TNF- alpha will also be evaluated in Specific Aim 2. This study will attempt to elucidate the mechanisms of neurotoxicity caused by chronic activation of the pathways for neuroimmune communication. The results will also provide critical information regarding the use of anti-inflammatory drugs for the treatment of CNS diseases.

TITLE	A Twin Study of Chronic Fatigue Syndrome in Sweden
P.I.	PEDERSEN, NANCY L.
GRANT NO.	1R01NS041483-01
Institution:	KAROLINSKA INSTITUTE (Sweden)

Despite considerable research, fundamental questions about CFS remain at best partially answered. These questions include its definition, validity, the degree to which it results from genetic versus environmental factors, the nature of the substantial comorbidity observed with other conditions, and the basis of the female preponderance. 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 collect data on approximately 32,000 adults aged 42-65 years (13,000 complete twin pairs) who are members of the population- based Swedish Twin Registry for persistent fatigue, several overlapping conditions (fibromyalgia, irritable bowel syndrome, tension headache, allergy/eczema, generalized anxiety disorder, and major depression), and a detailed medical history. Second, the medical records of all twins who appear to have CFS-like illness and a subset of those with "CFS-explained" will be requested via an efficient national retrieval system. Following expert review, these individuals will be classified in regard to the CDC CFS criteria. Obtaining these unique data will allow us to address a set of critical questions regarding CFS. First, we will estimate the prevalence of CFS and its common comorbidities (fibromyalgia, irritable bowel syndrome, tension headache, allergy/eczema, generalized anxiety disorder, and major depression) in one of the largest samples yet studied. Second, we will use a variety of multivariate techniques to derive an empirical typology of prolonged fatigue and to assess how this typology compares to the CFS definition. Third, we will quantify the genetic and environmental sources of variation for CFS and its comorbid conditions. Fourth, critically, we will examine the influence of gender on these sources of variation. Finally, we will analyze the patterns of comorbidity between CFS and fibromyalgia, irritable bowel syndrome, tension headache, allergy/eczema, generalized anxiety disorder, and major depression using multivariate twin analyses and thereby to estimate the extent of overlap between the shared and unique genetic and environmental sources of variation. In concert with other twin studies being conducted by the investigators and their collaborators, we hope to hasten progress in understanding the etiology of CFS by parallel studies in multiple populations. The current proposal has several unique aims and represents a cost-effective means to extend this work in an epidemiological sample that is arguably the best twin registry in the world.

TITLE	MOTOR LEARNING IN CFS--NEURAL DYSFUNCTION IMPLICATION
P.I.	SERVATIUS, RICHARD J.
GRANT NO.	5R01NS038337-03
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.

TITLE	Clinical Neurocardiology: Catecholamine Systems In Stress
P.I.	GOLDSTEIN, DAVID S.
GRANT NO.	1Z01NS002979-03
Institution:	

We conducted patient-oriented clinical research in neurocardiology. Studies focused on elucidating pathophysiologic mechanisms and developing novel diagnostic and therapeutic approaches for disorders involving altered regulation of catecholamine systems. These conditions result from dysfunction of the autonomic nervous system (dysautonomia) or abnormally decreased or increased production of the catecholamines, norepinephrine (NE), epinephrine (EPI), or dopamine (DA). Patients with autonomic failure in the setting of Parkinson's disease all had cardiac sympathetic denervation, detected by 6-[18F]fluorodopamine positron-emission tomographic scanning. In contrast, patients with multiple system atrophy, which can be difficult to distinguish clinically from Parkinson's disease, all had evidence for intact cardiac sympathetic nerve terminals. Even in the absence of autonomic failure, most patients with Parkinson's disease had evidence for localized or diffuse loss of cardiac sympathetic nerve terminals. Cardiac sympathetic denervation in Parkinson's was found to be independent of levodopa treatment and can arise from mutation of the gene encoding alpha-synuclein. In the diagnostic evaluation of pheochromocytoma, a clinically important tumor that produces catecholamines, plasma levels of metanephrines, metabolites of NE and EPI made in the tumor, provided a uniquely and virtually perfectly sensitive screening test. In patients with chronic orthostatic intolerance, a pattern of increased adrenomedullary hormonal system activity and inhibition of sympathetic nervous system activity ("sympathoadrenal imbalance") was found to precede tilt-induced and spontaneously occurring neurocardiogenic syncope. 6-[18F]Fluorodopamine positron-emission tomographic scanning successfully localized the tumor even in difficult cases. A combined neurogenetic and neurochemical approach holds great promise for understanding how particular mutations in familial diseases associated with increased production of NE (pheochromocytoma) or decreased production of NE (Menkes disease) relate to particular neurochemical and clinical manifestations.

NIAD

TITLE	Brain and Cardiovascular Studies
P.I.	NATELSON, BENJAMIN H.
GRANT NO.	5U01AI032247-110006
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.	5U01AI032247-110007
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.	5U01AI032247-119003
Institution:	UNIV OF MED/DENT NJ NEWARK
There is no text on file for this abstract.	

TITLE	MECHANISMS OF IMMUNOLOGICALLY MEDIATED FATIGUE
P.I.	PETERSON, PHILIP K.
GRANT NO.	5R01AI035110-07
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	MONOZYGOTIC TWINS WITH CHRONIC FATIGUE SYNDROME--PREDISPOSITION OR PERCEPTION?
P.I.	BUCHWALD, DEDRA S.
GRANT NO.	5U19AI038429-070005
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	POPULATION BASED TWIN STUDY OF CHRONIC FATIGUE SYNDROME
P.I.	SULLIVAN, PATRICK F.
GRANT NO.	5U19AI038429-070006
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.	5U19AI038429-070007
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--CLINICAL FACILITY
P.I.	BUCHWALD, DEDRA S.
GRANT NO.	5U19AI038429-079002
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	CORE--BIOSTATISTICAL AND DATA MANAGEMENT FACILITY
P.I.	ZEH, JUDITH
GRANT NO.	5U19AI038429-079001
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	Mechanisms of Rhinitis in CFS
P.I.	BARANIUK, JAMES N.
GRANT NO.	2R01AI042403-04A1
Institution:	GEORGETOWN UNIVERSITY

This abstract is not available.

TITLE	COGNITIVE BEHAVIORAL STRESS MANAGEMENT INTERVENTION FOR CFS
P.I.	ANTONI, MICHAEL H.
GRANT NO.	5U01AI045940-030002
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.	5U01AI045940-030004
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.	5U01AI045940-039003
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.	5R03AI045954-03
Institution:	NEW YORK MEDICAL COLLEGE
This abstract is not available.	

TITLE	ACTIVITY INTERVENTION FOR CHRONIC FATIGUE SYNDROME
P.I.	JASON, LEONARD
GRANT NO.	5R01AI049720-02
Institution:	DE PAUL UNIVERSITY

The primary purpose of this study is to evaluate the efficacy of the nurse delivered behavioral interventions of graded activity with cognitive therapy and graded activity alone in comparison to a cognitive therapy alone control condition in a target sample of 120 persons with CFS. This study will: 1) test the hypothesis that graded activity with cognitive therapy will yield significant improvements in physical and role functioning in comparison to the cognitive therapy alone control condition; and 2) test the hypothesis that graded activity alone will yield significant improvements in physical and role functioning in comparison to the cognitive therapy alone control condition. In addition, this study will test, as a secondary Aim, that graded activity alone will be as effective as graded activity with cognitive therapy in improving physical and role functioning in CFS. Since medical utilization rates for CFS patients are high and medical therapies for CFS have been largely unsuccessful, the study of a potentially effective behavioral intervention for the illness may offer an opportunity for a substantially improved quality of life in these debilitated patients.

NIMH

TITLE	Psychiatric Comorbidity in Chronic Fatigue Syndrome
P.I.	FRIEDBERG, FRED
GRANT NO.	1K23MH001961-01A1
Institution:	STATE UNIVERSITY NEW YORK STONY BROOK

The purpose of this application is twofold: 1) To provide a systematic plan for career development of the Candidate as a clinical researcher; and 2) to present a preliminary study application based on a sound research plan. The career development plan involves: a) taking graduate courses in advanced statistics and research methods, behavioral assessment, and ethical issues; and b) supervision by two mentors of the conduct of research by the Candidate. The Specific Aims of the preliminary study are to: 1) compare in vivo and traditional retrospective outcome measures in patients with chronic fatigue syndrome (CFS) in order to assess the ecological validity of traditional measures in both naturalistic outcome (NO) and clinical outcome (CO) studies; 2) test the hypothesis, via secondary data analysis in the CO study, that a clinically meaningful classification of CFS patients into high and low functioning subgroups can be made on the dimension of physical functioning and validated with its relationship to role functioning, CFS symptom severity, and psychiatric symptomatology; and 3) test the hypothesis, via secondary data analysis in the CO study, that graded activity with cognitive therapy is more effective for low function participants and that cognitive-behavioral coping skills treatment is more effective for the high function subgroup. The NO and CO studies involve cohorts of 100 and 120 patients, respectively. Data collection will include 21 (NO study) or seven (CO study) consecutive daily in vivo assessments of physical activity (actigraphy), energy, fatigue, and affect. In vivo assessments will take place at baseline and at a 24 month follow-up in the NO study, and at baseline, treatment termination, and three, six, and 12 month follow-up intervals in the CO study. The findings of this study will have important implications for clinical management of this debilitating illness.

TITLE	AUDITORY WORKING MEMORY IN CFS--AN FMRI STUDY
P.I.	LANGE, GUDRUN
GRANT NO.	5R01MH057272-03
Institution:	UNIV OF MED/DENT NJ NEWARK

This abstract is not available.

NIMH

TITLE	ACTIVITY INTERVENTION FOR CHRONIC FATIGUE SYNDROME
P.I.	JASON, LEONARD
GRANT NO.	5R01AI049720-02
Institution:	DE PAUL UNIVERSITY

The primary purpose of this study is to evaluate the efficacy of the nurse delivered behavioral interventions of graded activity with cognitive therapy and graded activity alone in comparison to a cognitive therapy alone control condition in a target sample of 120 persons with CFS. This study will: 1) test the hypothesis that graded activity with cognitive therapy will yield significant improvements in physical and role functioning in comparison to the cognitive therapy alone control condition; and 2) test the hypothesis that graded activity alone will yield significant improvements in physical and role functioning in comparison to the cognitive therapy alone control condition. In addition, this study will test, as a secondary Aim, that graded activity alone will be as effective as graded activity with cognitive therapy in improving physical and role functioning in CFS. Since medical utilization rates for CFS patients are high and medical therapies for CFS have been largely unsuccessful, the study of a potentially effective behavioral intervention for the illness may offer an opportunity for a substantially improved quality of life in these debilitated patients.

NCRR

TITLE	MUSCLE BLOOD FLOW AND CFS
P.I.	MCCULLY, KEVIN K.
GRANT NO.	5R01HL065179-03
Institution:	UNIVERSITY OF GEORGIA
This abstract is not available.	

TITLE	MODEL FOR INDUCTION OF CHRONIC FATIGUE STUDY
P.I.	JONES, JIM
GRANT NO.	5M01RR000051-401090
Institution:	UNIVERSITY OF COLORADO HLTH SCIENCES CTR
This abstract is not available.	

TITLE	CLINICAL BENEFIT OF MIDODRINE HCL IN PATIENTS W/ NEUROGENIC ORTHOSTATIC H
P.I.	BLOOMFIELD, DANIEL
GRANT NO.	3M01RR000645-30S10867
Institution:	COLUMBIA UNIVERSITY HEALTH SCIENCES
This abstract is not available.	

TITLE	HER RECEPTOR FAMILY, HEREGULIN AND LUNG DEVELOPMENT
P.I.	KERN, JEFFREY A.
GRANT NO.	7R01HL060165-03
Institution:	CASE WESTERN RESERVE UNIVERSITY

Identification of growth factor receptors and their specific activating ligands involved in lung development might aid in disease management by providing novel therapeutic approaches and targets for new drugs. In previous studies, my laboratory identified a novel growth factor receptor in the human lung, the human epidermal growth factor receptor 2 (HER2). This receptor is one member of a family of four membrane bound receptor tyrosine kinases (RTK) called HER1, HER2, HER3 and HER4. Their interaction with a specific activating ligand called heregulin (HRG) is important in the regulation of epithelial cell growth and differentiation. Our further studies showed that HER2, HER3 and HRG are expressed in the developing human, murine and rat lung, are temporally modulated, and are probably important in normal lung development. It is the overall goal of this study to ascertain the biological role of the HRG/HER system in the regulation of lung development and pulmonary epithelial cell proliferation. Specifically, this proposal hypothesizes that: 1) Activation of the high affinity HRG receptor (HER2/HER3 heterodimer) by its ligand (HRG) results in a proliferative signal for pulmonary epithelial cells, 2) Activation of the high affinity HRG receptor in pulmonary epithelial cells initiates a specific signal transduction cascade that is essential for pulmonary epithelial cell growth and differentiation, and 3) Modulation of the HRG/high affinity HRG receptor in vivo will result in lack of normal lung development. We will test this hypothesis by: 1) Determining the role activation of the high affinity HRG receptor, the HER2/HER3 heterodimer, has in human fetal lung development in vitro, 2) Defining the signal cascade initiated after HRG-induced HER activation in pulmonary epithelial cells, and 3) Developing transgenic mouse strains with lung-specific, developmentally inappropriate HRG expression, or a dominant-negative HRG receptor to determine the developmental effect of aberrant HRG receptor activation on lung growth and development in vivo. These studies will be performed in vitro using a human fetal lung explant model system and pulmonary epithelial cell lines, and in vivo with the development of transgenic mouse strains.

TITLE	CHRONIC FATIGUE IN POST LYME DISEASE
P.I.	KRUPP, LAUREN
GRANT NO.	5M01RR010710-040029
Institution:	STATE UNIVERSITY NEW YORK STONY BROOK

The primary objective of STOP-LD is to determine if parenteral antibotic treatment is an effective treatment for patients with chronic fatigue following Lyme Disease. If the study fundings indicate that patients improve with antibiotic therapy according to the STOP-LD outcome measures, it will set an important precedent for treatment of Post Lyme Syndrome (PLS) and provide support for a syndrome pathogenesis involving chronic infection. If no difference between antibiotic and placebo therapy is observed, this will be important objective data suggesting the inappropriateness of repeated courses of antibiotic therapy for PLS.

TITLE	NEUROENDOCRINOLOGY OF MASTICATORY MUSCLE DISORDERS
P.I.	YOUNG, ELIZABETH ANN.
GRANT NO.	5R01DE011972-05
Institution:	UNIVERSITY OF MICHIGAN AT ANN ARBOR

The temporomandibular disorders (TMDs) are a complex group of conditions involving masticatory muscles and/or temporomandibular joints and characterized by chronic facial pain. The etiology and pathogenesis of TMDs are multifactorial, including a strong association with depression and the occurrence of environmental stressors, with a strong predominance of women with these disorders (75-84%). It is known that dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, the main stress hormone axis, occurs in both depression and stress-related disorders. Recent evidence also demonstrates HPA dysregulation in other conditions related to TMDs: in particular, in fibromyalgia. This is a condition of generalized myalgia with a great deal of clinical overlap with masticatory muscle disorders (MMDs), a major sub-group of TMDs. Fibromyalgia also shows a similar high female predominance and is associated with high rates of depression and stress. Furthermore, there is evidence of important gender differences in HPA axis function resulting in an increased stress responsiveness and susceptibility to HPA dysregulation in women, thus providing an explanation for the high female predominance of fibromyalgia, depression and MMD. This study will examine the comorbidity of MMD and disorders associated with HPA stress axis dysregulation including fibromyalgia and stress-related psychiatric disorders, including depression, and test the hypothesis that women with MMD have an underlying HPA axis abnormality similar to that which occurs in fibromyalgia, namely HPA axis hypofunction, which is the underlying pathophysiological basis of both disorders. HPA function will be studied in women with MMD, (with and without comorbid fibromyalgia and depression) compared to normal controls, in terms of circadian and pulsatile patterns of basal cortisol secretion, using an intensive 24-hour plasma cortisol sampling paradigm. Women will be studied during both follicular and luteal phases of the menstrual cycle to test the hypothesis that there will be menstrual cycle-phase related fluctuations in symptoms and HPA axis function. These multidisciplinary studies will provide an understanding of the pathophysiological basis of the relationship of MMD to seemingly disparate conditions such as fibromyalgia and depressive disorders, as well as the higher prevalence in women, leading to a more rational basis for diagnosis and treatment of MMD.