2002 NIH Funded CFS Research

NHLBI

TITLE	Transcriptional Regulation of E-Selectin
P.I.	COLLINS, TUCKER O.
GRANT NO.	2R01HL045462-13
Institution:	CHILDREN'S HOSPITAL (BOSTON)

Vascular endothelium forms a dynamic interface between blood elements and peripheral tissues. Endothelial cells can undergo changes in function that are critical to normal physiological processes, and non- adaptive alterations that are important in the pathogenesis of vascular disease, including the expression of adhesion molecules. E-selectin is an endothelial-leukocyte adhesion molecule that plays a role in recruitment of neutrophils to sites of inflammatory responses. Its expression is dramatically increased by inflammatory cytokines. We have been examining cytokine-induced expression of the E-selectin gene as a model for how gene expression is activated in the endothelial cell. Analysis of the E-selectin promoter reveals a small cytokine response region consisting of three nuclear factor-kappaB (NF-kappaB) elements and a CRE/ATF-like site. The transcription factors that recognize these elements are targets of signaling events leading to induced gene expression. The working hypothesis is that the E-selectin cytokine- induced transcriptional enhancer consists of an enhanceosome, or a specific spatial arrangement of transcription factors and architectural proteins. We propose to study how this structure directs the recruitment of co-activators and chromatin remodeling factors that result in the induction of gene expression. Following induction, the expression of the gene is diminished by an active process that may involve the recruitment of co-repressors. By characterizing the activation and repression of the E-selectin gene it may be possible to elucidate the transcriptional control processes that activate other inducible genes and convert the quiescent endothelium into a dysfunctional vascular element. Such information may provide novel strategies for therapeutic approaches to the important problem of vascular disease.

TITLE	Reactive Species in Vascular Disease-Injury Mechanisms
P.I.	ISCHIROPOULOS, HARRY
GRANT NO.	2R01HL054926-05A1
Institution:	CHILDREN'S HOSPITAL OF PHILADELPHIA

Experiments in this application will examine the molecular mechanisms responsible for the modulation of cellular metabolism and resistance to oxidants by endogenous nitric oxide (NO). Published data indicated that NO either directly mainly by reversible S-nitrosylation of critical cysteine residues or by elevating cGMP levels modulates the adaptive responses that render cells resistant to oxidative stress and apoptosis. However, the majority of the cellular models rely upon the deliver of NO by NO donors or by the induction of the inducible nitric oxide synthase (NOS). To study the contribution of NO generated by the low output endothelial NOS in the cellular protection against oxidants, we utilized ECV3O4 cells transfected with endothelial NOS. The transfected cells generated sufficient NO to induce elevation of cGMP in smooth muscle cells in an L-NAME inhabitable manner. Using this well-defined model preliminary data revealed that NO regulates the steady state of ATP, the flux of glucose by the glycolytic and pentose phosphate pathways and respiration. Moreover, this dynamic regulation of metabolism and mitochondrial bioenergetics was associated with an increased resistance to H2O2 exposure. Exposure to H2O2 at 50-100 pM induced a delayed cell death (18 hours after exposure) to nearly 50 percent of ECV3O4 but less than 20 percent in the ECV3O4-eNOS cells. Inhibition of NO production ameliorated the protective effect and restored the steady state levels of ATP and glucose fluxes. Preliminary data using human pulmonary artery endothelial cells confirmed the NO-dependent protection against H202 induced delayed cell death. These preliminary data together with scarce published data on the ability of NO to regulate metabolism suggest a previous unrecognized function of NO that may causally relate to adaptation against oxidative stress. We propose that the generation of low levels of NO by eNOS is sufficient to dynamically regulate cellular glucose metabolism and respiration providing a primary and previously unrecognized molecular mechanism for the NO-induced protection against oxidative stress. To examine these hypotheses we propose the following specific aims: (1) define the molecular mechanism(s) of nitric oxide-mediated regulation of cellular metabolism; (2) investigate the causal association between nitric oxide-dependent alterations in metabolism with the adaptation to oxidative stress; and (3) examine if endogenous nitric oxide regulation of mitochondrial respiration and mitochondrial function is responsible for the protection against oxidative stresses. Experiments in the first aim are focused on the allosteric, covalent and other regulatory functions of NO in critical enzymes that catalyze essential and irreversible steps in the glycolytic pathway and TCA cycle. The second aim will utilize biochemical, pharmacological and molecular approaches to provide evidence for the potential causal relationship between NO-mediated regulation of metabolism and resistance to oxidative stress. The third aim examines the importance of NO-regulated mitochondrial respiration and function in protecting cells from oxidant exposures and typical inducers of apoptosis. Overall the proposed experiments will evaluate in a systematic manner the critical role of endogenously generated NO as a mediator of cellular metabolism and respiration that enables cells to resist oxidative stress.

TITLE	Molecular Basis for Protein-Phospholipid Interaction
P.I.	LOMASNEY, JON W.
GRANT NO.	2R01HL055591-06
Institution:	NORTHWESTERN UNIVERSITY

This application seeks to extend a program that has demonstrated the role of phospholipids as important ligands that regulate protein function. Phosphatidylinositol 4,5-bisphosphate (PIP2) and phosphatidylinositol 3,4,5-triphosphate (PIP3) have been implicated in a number of fundamental cellular processes including acting as a targeting ligand for PH domain containing proteins, as an activator of signaling molecular like phospholipase D, phospholipase C (PLC), and the small G protein ARF; as a regulator of the actin cytoskeleton directing cytokinesis in Dictyostelium, and acting as a regulator of endo and exocytosis. Since these specific ligand species have important regulatory roles in processes such as membrane trafficking and cell signaling, localization of polyphosphoinositides (PIPn) within the cell is important. The first specific aim will characterize microdomains of the plasma membrane that contain PIP2 and PIP3 using genetic and biochemical approaches. It is hypothesized that specific protein complexes are involved in transporting and maintaining locally high concentrations of these (PIPn). The molecular mechanisms responsible for creation of functional compartments of bioactive lipid will be determined. The second specific aim will investigate the role of the acyl groups of phospholipids in regulating protein function. It is hypothesized that proteins like PLC delta 1 interact with the hydrophobic portions of phospholipids as well as the hydrophilic head group. Several modified forms of PIP2 such as di-C4, di-C8, and di-C16 will be assessed for activity in vitro using detergent mixed micelles with pure recombinant PLC delta 1. The specificity for acyl chains in vivo will be assessed by supplementing media with fatty acids and delivering PIP2 derivatives using polyamine carriers and looking at enzyme activity. The third specific aim will describe the allosteric effects of PS at the C2 domain of PLC delta 1. Kinetic studies will be performed in detergent mixed micelles using the soluble substrate 1,2 solution without an interface. The fourth specific aim will test the hypothesis that the acyl chains of phosphatidylserine are vital to the stimulation of PLC delta 1 via the C terminal C2 domain. Amino acid residues involved in acyl chain interactions will be identified. Because the enzymatic specificity for fatty acids is at best only moderate, the fatty acid composition of phospholipids is easily influenced by diet. Therefore, we believe that diet can influence the function of proteins and contribute to environmental phenotypes. Since many diseases that afflict man have environmental components, the DNA-protein paradigm cannot explain all human afflictions. We hypothesize that the lipids play a role in the development of human disease.

TITLE	MECHANISMS BY WHICH IGF-I STIMULATES SMOOTH MUSCLE CELLS
P.I.	CLEMMONS, DAVID R.
GRANT NO.	2R01HL056850-06
Institution:	UNIVERSITY OF NORTH CAROLINA CHAPEL HILL

The purpose of these studies IS to analyze the molecular mechanisms by which insulin-like growth factor-1 (IGF-l) stimulates smooth muscle cell (SMC) migration and replication. SMC synthesize IGF binding protein- 4 (IGFBP-4) and an IGFBP-4 protease. IGFBP-4 inhibits IGF-l binding to receptors and the protease facilitates its release. These studies will focus on expressing pure fibulin 1-C which has IGFBP-4 protease activity, identifying the factors that regulate its synthesis and activation and determining its physiologic role in releasing IGF-l to SMC. A protease resistant form of IGFBP-4 will be used to assess the importance of release of IGF-l into the pericellular space for atherosclerotic lesion development. Several integral membrane proteins regulate the ability of target cells such as SMC to respond to IGF-l. These include the IGF-l receptor, the aV133 integrin, integrin associated protein (lAP) and SHPS-l. To study the interaction between lAP and aV133 we will prepare lAP mutants that do not bind to aVI33, express them in SMC and determine if cells expressing these mutants have an altered biologic response to IGF-l. Since truncation of aV alters aVBeta3 binding to lAP we will utilize cells expressing a truncated aV mutant to determine how this alters IGF-l stimulated binding to lAP. Since changes in lAP binding within lipid domains of cell membranes are important for controlling whether it binds to a we will determine how IGF-l facilitates this process. Atherosclerotic lesions will be analyzed to determine if IGF-l stimulates the association of lAP with avBeta3 in vivo. To determine how ligand occupancy of lAP modulates cellular responsiveness to IGF-l, we will prepare an lAP mutant that cannot bind to its principle ligand thrombospondin-1 (TSP-i) and determine if cells that express this mutant have altered biologic responses to IGF-l. We will analyze the mechanism by which TSP-i binding to lAP is altering IGF receptor function and determine if TSP-i binding to lAP is functioning through SHPS-1 to alter the rate at which the IGF-l receptor is dephosphorylated. The results of these studies should define multiple new molecular mechanisms by which IGF-l functions coordinately with extracellular matrix proteins to activate its receptor and stimulate SMC replication and migration. The results may suggest novel strategies for interfering with these processes to alter the progression of atherosclerosis.

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.	5R01HL065668-03
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.

TITLE	Circulatory Dysfunction in Chronic Fatigue Syndrome
P.I.	STEWART, JULIAN M.
GRANT NO.	5R01HL066007-02
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	Skin Cooling to Improve Orthostatic Tolerance
P.I.	CRANDALL, CRAIG G.
GRANT NO.	1R01HL067422-01A1
Institution:	UNIVERSITY OF TEXAS SW MED CTR/DALLAS

Post-space flight orthostatic hypotension/intolerance occurs in 25 to 66 percent of crew members upon returning to a 1 G environment. The mechanism(s) causing this response are not completely understood. Identification of countermeasures to reduce the incidence of orthostatic intolerance associated with space flight is paramount to NASA's mission. One such countermeasure may be skin surface cooling. In light of this, three specific objectives will be accomplished by the proposal work: 1) Identify an optimal skin surface cooling paradigm that causes the largest increase in autonomic responses (i.e. stroke volume, blood pressure, sympathetic nerve activity, etc.) without causing shivering or altering motor function. 2) Identify the mechanisms by which skin surface cooling increases the aforementioned autonomic responses resulting in improved tolerance to orthostatic stress. 3) Identify whether skin surface cooling is an effective countermeasure to improve orthostatic tolerance in men and women following simulated microgravity exposure using the head-down tilt bed rest model. Upon completion of the proposed studies important information will be provided that will be beneficial for both operational and safety concerns for astronauts, as well as to individuals who suffer from idiopathic orthostatic intolerance.

TITLE	Endothelial Cell Dysfunction in Oxidative Stress Models
P.I.	CALDWELL, ROBERT W.
GRANT NO.	1R01HL070215-01
Institution:	MEDICAL COLLEGE OF GEORGIA

Endothelial cell dysfunction is a primary basis of cardiovascular disease including diabetes mellitus. Evidence suggest that supplemental L-arginine (L-arg) is therapeutically useful in reversing endothelial dysfunction and treating cardiovascular disease, but the mechanism of this effect is unknown. Therefore, we are studying the impact of oxidative injury on endothelial cell transport of L-arg and how it relates to endothelial dysfunction by using experimental models of diabetic coronary artery disease. The normal function of the vascular system depends critically on nitric oxide (NO) production by vascular endothelial cells (EC). However, in conditions associated with oxidative vascular injury such as diabetes mellitus, atherosclerosis, and hyperhomocystememia, excess formation of reactive oxygen species can lead to endothelial dysfunction and reduction in NO bioavailability. NO is produced by NO synthase (NOS) from its substrate L-arg. When L-arg availability to NOS is limiting, NOS acts principally upon 0, to form superoxide (O-), which rapidly combines with NO to form peroxynitrite (ONOO). ONOO- and 02+formation can lead to further formation of O NOS due to oxidation of BH4 (tetrahydrobiopterin), a critical co-factor for NOS. In EC, supply of L-arg to NOS depends mainly on the function of a specific transporter, system y+. Our data show that continued NO oxidant exposure inhibits system y transport of L-arg, reducing availability of L-arg and leading to formation of O2 This EC pathology is reversed with supplemental L-arg. We hypothesize that endothelial cell injury mediated by reactive oxygen species (ROS) reduces L-arg transport function. This reduces L-arg uptake and shifts NOS activity from NO production to O2 production, leading to further compromise of the L-arg transporter. These deleterious effects can be prevented with supplemental L-arg. Our specific aims will test these hypotheses and further characterize the regulation of L-arg transporter. Aim 1. HYPOTHESIS: Chronic exposure 10 ROS causes dysfunction of the L-arg transporter. To test this hypothesis, we will determine the effects of chronic exposure to NOS agonists, NO donors, 02+-, ONOO- on uptake of [3H]L-arg in A) human coronary artery ECs and B) isolated rabbit hearts perfused by the Langendorff procedure. Aim 2. HYPOTHESIS.- Reduction of L-arg uptake shifts NOS activity from NO production to O - production leading to further compromise of the L-arg transporter. We will use the oxidant treatment protocols of aim 1 to correlate basal and NOS agonist-stimulated EC production of NO, O2 - and ONOO- with L-arg transport activity. Aim 3. HYPOTHESIS: Oxidant exposure alters transporter protein expression subcellular distribution and/or molecular interactions with eNOS. Recent studies indicate the principal supply of L-arg to eNOS occurs within caveolae where the L-arg transporter protein CAT1 interacts with eNOS. Thus, oxidant exposure may inhibit L-arg transport by altering CAT! expression levels, subcellular compartmentalization and/or protein-protein interactions with eNOS. Interactions of these systems will be tested by experiments exposing HCAEC to the above oxidant treatments and determing the effects on CAT expression, subcellular distribution and molecular interactions with eNOS by using immunoprecipitation, immunoblotting, subcellular fractionation and confocal microscopy. Aim 4. HYPOTHESIS: High glucose/ diabetes causes endothelial dysfunction and reduces the bioavailability of NO by increasing formation of O2 - and ONOO which alters function of the L-arg transporter, oxidizes tetrahydrobiopterin, and shifts eNOS activity from NO to 02 - production. This hypothesis will be tested by the following experiments: A) determining the effects of high glucose/diabetes on L-arg transport in relation to eNOS expression and activity and formation of NO of 02 - and ONOO- in HCAEs exposed to high glucose or control conditions and in the coronary circulation isolated from diabetic rabbit hearts; and B) determining whether supplemental L-arg is effective in preventing the effects of high glucose/diabetes on the above parameters.

NINCDR

TITLE	COMPREHENSIVE CENTER FOR INFLAMMATORY DISORDERS
P.I.	FLOOD, PATRICK M.
GRANT NO.	3P60DE013079-03S1
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.

TITLE	COMPREHENSIVE CENTER FOR INFLAMMATORY DISORDERS
P.I.	FLOOD, PATRICK M.
GRANT NO.	5P60DE013079-04
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.

TITLE	Brain and Cardiovascular Studies
P.I.	NATELSON, BENJAMIN H.
GRANT NO.	5U01AI032247-120006
Institution:	UNIV OF MED/DENT NJ NEWARK

Two groups of patients with chronic fatigue syndrome have been identified. One group has a putative neurological cause for the illness and a second group a putative cardiovascular cause. The index of neurologic dysfunction is the presence of abnormalities on cognitive testing and the index for cardiovascular dysfunction is the presence of a low stroke volume. The applicants acknowledge the possibility of overlap of the two conditions as well as the presence of a group exhibiting neither abnormality. Thus, in any one project, 4 groups of patients with chronic fatigue syndrome will be tested. These will be compared to a control group of sedentary individuals. Five studies are planned. Study 1 assesses the constitution of spinal fluid for markers of inflammation as well as for 5-HIAA, MHPG and substance P. Study 2 proposes to evaluate changes in the plasma prolactin, ACTH and cortisol in response to the intravenous infusion of a serotonin uptake blocker. Study 3 proposes to use xenon CT scanning to assess cerebral blood flow. Study 4 proposes to use radionuclide ventriculography to assess cardiac function at rest and during emotional, orthostatic and physical stress. Study 5 proposes to lower body negative pressure to provide a graded assessment of orthostatic tolerance.

TITLE	Physiological Challenges in CFS
P.I.	LA MANCA, JOHN
GRANT NO.	5U01AI032247-120007
Institution:	UNIV OF MED/DENT NJ NEWARK

Extending a series of observations regarding the hypothesis that CFS patients can be stratified into putative neurologic and cardiologic groups, this project intends to use exercise and hypoxia as a physiologic stressors to perturb acute cognitive function. The underlying hypothesis is that subgroups of these patients have cognitive dysfunction that is not clinically apparent in a basal state. The investigators further hypothesize that in the face of physiologic stresses of maximal exercise, submaximal exercise and mild hypoxia mimicking 12,000 feet altitude, cognitive changes will become apparent. Subjects will undergo: ANAM Cognitive Test battery- following asymptotic training. Submaximal exercise tests to assess gas-exchange threshold; then sustained workload to 70 percent of the gas-exchange threshold. Ambulatory Activity Monitoring: 5 days prior and 14 days following exercise. Hypoxic challenge at 85 percent measured oxygen saturation. With the submaximal exercise challenge and the hypoxic challenge, subjects will have a comprehensive set of non-invasive physiologic investigations including photoplethsymography, impedance cardiography, and occlusion venous plesthymography. They will sequentially undergo the ANAM cognitive test battery in a pattern that includes intra-subject controls for order effects and training effects. Data will be analyzed with the group stratified by the operational definitions the putative groups noted in the core discussion.

TITLE	RENEWAL OF THE NEW JERSEY CFS CRC
P.I.	NATELSON, BENJAMIN H.
GRANT NO.	5U01AI032247-12
Institution:	UNIV OF MED/DENT NJ NEWARK

We propose to continue the work of our CFS CRC. The central theme and goal of the Center is to stratify CFS patients based on differences in cardiovascular and neuropsychological function. The purpose of our Center will be to continue to use the syndromic approach to identify subgroups of patients with different putative organic causes for their fatiguing illness. In the past grant cycle, we have identified two such -- one implicating the brain and another implicating abnormalities in peripheral cardiovascular function. We plan to bring in CFS patients and categorize them based on the variables that track these putative organic causes -- namely cognitive dysfunction and cardiac stroke volume. By using a median split approach, we will have data from 4 groups of patients and can make a priori hypotheses about which group will show the biggest differences from our sedentary healthy controls during experimental testing. The work we propose begins at the molecular level of serotonin receptor function and spinal fluid constitution, moves on to the physiological level in experiments on brain blood flow, on the structure and function of the heart, and on orthostatic intolerance and continues to the system level in a longitudinal study that follows the illness patterns of different subsets of CFS patients over time. Thanks to prior NIAID support, we have put together a broad team of experts -- all with major interests in understanding CFS. The group is headed by a neurologist-scientist and is comprised of psychologists, physiologists expert in behavioral medicine, exercise and activity assessments, and a superb statistician. New collaborations were initiated - one with a physician in Germany who is expert in autoantibodies and another with an NIMH researcher expert in central factors in fatiguing illness. We propose a three tiered strategy for the next 5 years of our Center's activities. First, we will use ideas synthesized from data generated from our original Center to fuel new studies aimed at understanding the abnormalities and/or causes of CFS. The second tier uses probes known to uncover subtle abnormalities in brain and cardiovascular function. The third tier is a longitudinal study of CFS to determine the pattern of illness over time and how illness and psychosocial factors interact over time.

TITLE	MONOZYGOTIC TWINS WITH CHRONIC FATIGUE SYNDROME--PREDISPOSITION OR PERCEPTION?
P.I.	BUCHWALD, DEDRA S
GRANT NO.	5U19AI038429-080005
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	CHILDREN OF CHRONIC FATIGUE SYNDROME PATIENTS
P.I.	SMITH, MARK
GRANT NO.	5U19AI038429-080007
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.	5U19AI038429-089002
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.	5U19AI038429-089001
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.	5R01AI042403-06
Institution:	GEORGETOWN UNIVERSITY

This abstract is not available.

TITLE	COGNITIVE BEHAVIORAL STRESS MANAGEMENT INTERVENTION FOR CFS
P.I.	ANTONI, MICHAEL H.
GRANT NO.	5U01AI045940-040002
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.	5U01AI045940-040004
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.	5U01AI045940-049003
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	ACTIVITY INTERVENTION FOR CHRONIC FATIGUE SYNDROME
P.I.	JASON, LEONARD
GRANT NO.	5R01AI049720-03
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.

TITLE	Viral dsRNA as a Mediator of Chronic Muscle Diseases
P.I.	TAM, PATRICIA E.
GRANT NO.	1R01AI051270-01
Institution:	UNIVERSITY OF MINNESOTA TWIN CITIES

Enteroviruses have long been suspected as potential etiologic agents of chronic muscle disease. Although they are not known to cause persistent infections, persistent enterovirus RNA has been detected in some patients. Experimental models have shown that enteroviral RNA assumes a double-stranded conformation (dsRNA) as part of its mechanism for persistence in muscle. However, the global effect of low levels of viral dsRNA in a long-lived tissue like skeletal muscle is unknown. This proposal is part of a long-range goal to understand the role of infectious agents in the pathogenesis of chronic muscle diseases such as chronic fatigue syndrome and the idiopathic inflammatory myopathies. The central hypothesis of this application is that low-level persistence of viral dsRNA is pathogenic for muscle. This hypothesis was formulated based on evidence from a mouse model that links coxsackievirus B1 (CVB1) RNA persistence to the development of chronic inflammatory myopathy. The rationale for the proposed research is that a lack of knowledge regarding the type of pathology caused by persistent enterovirus dsRNA has hampered investigations into the etiology and pathogenesis of these diseases. The central hypothesis will be tested through the pursuit of the following two specific aims: (1) establish a transgenic model to achieve regulated expression of CVB1 dsRNA in muscle and characterize the clinical disease associated with its expression, and (2) identify the diagnostic signature of muscle pathology mediated by viral dsRNA. The proposed work is innovative because it represents a novel way of viewing chronic disease caused by enteroviruses-namely, that it is the persistent dsRNA itself and not solely the acute infection that mediates pathology. The outcome of these studies is expected to lead to the identification of a diagnostic signature for chronic muscle diseases caused by persistent viral dsRNA. The results will advance the development of better tools for the epidemiologic study, diagnosis, and treatment of diseases where enterovirus infection has been implicated.

NIMH

TITLE	Psychiatric Comorbidity in Chronic Fatigue Syndrome
P.I.	FRIEDBERG, FRED
GRANT NO.	5K23MH001961-02
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.

NIAMS

TITLE	Are Fibromyalgia and Chiari I Malformation Related?
P.I.	BUCHWALD, DEDRA S.
GRANT NO.	1R01AR047678-01A1
Institution:	UNIVERSITY OF WASHINGTON

Fibromyalgia *(FM) is a common condition of unknown etiology characterized by widespread muscle pain, sleep disturbances, fatigue, and various subjective neurological complaints. FM also frequently co-occurs with chronic fatigue syndrome, a condition similar to FM, whose hallmark is persistent, disabling fatigue. Many mechanisms for FM have been postulated but none has gained widespread acceptance or withstood the rigors of repeated scientific inquiry. Chiari I malformation (CIM), a hindbrain malformation associated with impairment of cerebral spinal fluid (CSF) flow, and syringomyelia, a cavitation of the spinal cord found in up to 80 percent of CIM patients, are neurological disorders. Although CIM patients typically seek medical attention for valsalva or exercise-related headaches, some present with non-specific complaints that are difficult to associate with CIM or syringomyelia. Common misdiagnoses for CIM include migraine, psychiatric disorder, multiple sclerosis, and FM. Successful treatment for symptomatic CIM patients, with or without syringomyelia, involves surgery to correct the presumed underlying pathophysiology by normalizing CSF flow in the hindbrain and enlarging the posterior fossa of the cranium. The overall safety and efficacy of the most common approach, a posterior fossa craniectomy and cervical laminectomy to expand the posterior fossa volume, is well supported in the literature. Recently, some FM patients have been treated with a posterior fossa and cervical operation. This procedure, performed by a select group of neurological surgeons, has attracted the attention of patients, the media, and the medical community. Hundreds, perhaps several thousand, of these operations have been performed without any scientific support for the safety or efficacy of this intervention in FM. The purpose of this study is to establish the relationship of hindbrain anomalies and cervical cord problems to FM. The Specific Aims are to: 1) determine the prevalence of CIM and cervical syringomyelia among patients with FM (with and without CFS) and pain- and fatigue-free controls using magnetic resonance (MR) imaging; 2) compare the clinical correlates and physical examination findings in these FM patients with and without CIM. There are plans to gather information on symptoms, and perform blinded neurological and MR examinations in 213 FM patients and 71 pain- and fatigue-free control subjects. MR sequences will quantitate posterior fossa anatomy, posterior fossa CSF volume, tonsillar position, and cervical spinal cord and canal pathology. To measure physiological parameters such as CSF velocity and direction of flow in the craniocervical junction, there are plans to employ cardiac gated phase-contrast cine-MR imaging. This study will assess the usefulness of MR imaging in the evaluation of FM patients with and without CFS, and may identify those who might benefit from surgery for hindbrain abnormalities and dissuade others from undergoing a potentially harmful intervention.*

NINR

TITLE	ACTIVITY INTERVENTION FOR CHRONIC FATIGUE SYNDROME
P.I.	JASON, LEONARD
GRANT NO.	5R01AI049720-03
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	PHOSPHOCREATINE RECOVERY IN WOMEN W/ CHRONIC FATIGUE SYNDROME
P.I.	MCCULLY, KEVIN
GRANT NO.	5P41RR002305-190029
Institution:	UNIVERSITY OF PENNSYLVANIA

In Utero surgical techniques for the reversal of anatomical malformations are developed in small mammalian models. The design of new techniques suffers from lack of non-invasive pre- and post-surgical fetal monitoring. We have applied high resolution MRI to in-vivo, in-utero imaging of a rat model for Congenital Diaphragmatic Hernia (CDH). CDH is a developmental anomaly which involves incomplete closure of the diaphragm, herniation of the liver and abdominal viscera into the thoracic cavity, and lung hypoplasia. Eight dams were imaged on days 19-22 of gestation (once a day) to diagnose the presence or absence of CDH and monitor the effects of surgery. Those who were shown to be CDH+ on day 19 underwent immediate surgical tracheal ligation to reverse pulmonary hypoplasia and force the abdominal contents from the thoracic cavity. 39 rat fetuses were imaged using a multislice, T2 weighted, fast spin echo sequence on a 4T whole body imaging system (GE, Signa). Pathology and results of surgery were confirmed post-mortem by high resolution imaging (9.4T) and subsequent microscopic dissection. This information will help in the use and development of in utero intervention for treatment of congenital abnormalities.

TITLE	PAIN PERCEPTION AND HEALTH CARE SEEKING BEHAVIOR IN FIBROMYALGIA
P.I.	BRADLEY, LAURENCE A.
GRANT NO.	5M01RR000032-420582
Institution:	UNIVERSITY OF ALABAMA AT BIRMINGHAM

The initial purpose of this project was to examine abnormal pain perception and health care seeking behavior among persons with fibromyalgia (FM). Our initial subject groups consisted of 66 rheumatology clinic patients with FM, 39 community residents with FM who had not obtained medical care for their painful FM symmptoms in the past 10 years (i.e., nonpatients), and 39 healthy controls recruited from the community. We found that both patients and nonpatients with FM show significantly lower pain threshold levels and produce significantly higher scores on an index of sensory discrimination than healthy controls. These findings were replicated at 1- and 2-year followup assessments. These findings indicated that abnormal pain perception is associated with FM independently of health care seeking behavior. Moreover, it was found that lifetime history of psychiatric disorders was the best psycho-social predictor of obtaining health care at a tertiary care, rheumatology clinic for FM symptoms, i.e., greater psychiatric morbidity was associated with health care seeking. This indicated that the high levels of psychiatric morbidity seen in tertiary care clinic patients with FM is more strongly related to health care seeking than to the disorder itself. This project has been renewed by the NIH for another four years. The purpose of the second cycle of the project is to examine functional brain activity in three groups of subjects during resting conditions and during exposure to an acute painful stimuluus. These groups are 30 patients with fibromyalgia, 30 patients with chronic fatigue syndrome, and 30 healthy controls. Functional brain activity is assessed by single photon emission computed tomographic imaging. Four subject protocols have been completed at present. It is anticipated that patients with fibromyalgia will show inhibited funtional brain activity, relative to patients with chronic fatigue syndrome and controls, in the thalamus and caudate nucleus during resting conditions and during painful stimulation. However, it also is expected that the fibromyalgia patients, compared to the other subject groups, will show higher levels of functional brain activity in the anterior cingulate cortex during painful stimulation.

TITLE	CHILDREN OF CHRONIC FATIGUE SYNDROME PATIENTS
P.I.	SMITH, MARK
GRANT NO.	5U19AI038429-080007
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	HPA AXIS DYSREGULATION IN FIBROMYALGIA
P.I.	CROFFORD, LESLIE J.
GRANT NO.	5M01RR000042-421009
Institution:	UNIVERSITY OF MICHIGAN AT ANN ARBOR

This abstract is not available.

TITLE	STRESS, ADRENERGIC AND INFLAMMATORY FACTORS IN 4 DISORDERS
P.I.	LIGHT, KATHLEEN C.
GRANT NO.	5P60DE013079-040008
Institution:	UNIVERSITY OF NORTH CAROLINA CHAPEL HILL

Chronic fatigue syndrome (CFS), Temporomandibular Disorder (TMD) and Fibromyalgia (FM) are common chronic disabling disorders whose pathogenesis and treatment are not well understood, but which share four characteristics: sensitivity to life stress, signs of pain system dysregulation, psychological distress and negative affect, and possible alteration of inflammatory mediators. The focus of the present investigation is to compare 40 patients meeting accepted diagnostic criteria for each of these disorders with 40 age- and gender-matched healthy controls and with 40 patients diagnosed criteria for each of these disorders with 40 age- and gender-matched healthy controls and with 40 patients diagnosed with Rheumatoid Arthritis (RA), the prototypical chronic inflammatory disorder. To determine whether there is evidence of dysregulation of autonomic (particularly beta-adrenergic function, hypothalamic-pituitary adrenocortical function (HPA), endogenous opioids, and inflammatory cytokine responses, these interacting physiological systems will be assessed during baseline and in response to two standardized stressors, a speech about interpersonal conflict and tourniquet-induced ischemic arm pain. Prior research has confirmed beta-adrenergic mediation of stress-induced changes in immune parameters. Thus, each subject will be studied twice, once after placebo and once after acute pretreatment with the non-selective beta-receptor antagonist, propranolol, to confirm the hypothesized involvement of beta-receptor activity in the dysregulated responses of the CFS, TMD and FM groups. In a second study, these same patients will be recruited to enter a placebo-controlled, double-blind cross-over treatment trial (6 weeks) of propranolol's potential benefits in normalizing responses to lab stressors and real life demands, in decreasing pain hypersensitivity, and improving somatic and psychological symptoms. A novel aspect of these studies will be their focus on the relationships between HPA axis function, autonomic function and effects upon IL6, IL1beta, and TNFalpha, the cytokines forming the central cascade in initiation of the inflammatory response. This investigation will provide important and needed assessment of basic physiological alterations, as well as more concrete tests of the contribution of stress exposure, in CFS, TMD and FM patients. Further, by clarifying the hypothesized role of beta-adrenergic activity and benefits of beta-blockade, it also provides a starting point for research on more effective medical treatment in disorders which have been medically difficult to manage.

TITLE	RESPONSIVENESS OF THE AGING CIRCADIAN CLOCK TO LIGHT
P.I.	BENLOUCIF, SUSAN J.
GRANT NO.	5R01HL067604-03
Institution:	NORTHWESTERN UNIVERSITY

The investigator's long-term goal is to understand the basis of and develop effective therapies for chronic sleep disturbances in older adults. One common sleep disorder in older adults is advanced sleep phase, accompanied by sleep maintenance insomnia and early morning awakenings. This can shorten the total sleep time and lead to daytime fatigue and impaired performance. The advance in sleep is associated with an advances in the timing of the circadian core body temperature rhythm which suggests an advance in the timing of the circadian clock. The cause of this advance is unknown. Preliminary date from the investigators laboratory suggests that elderly subjects do not phase delay following exposure to 4000 lux for 3 hours before the temperature minimum, a time that usually does delay the rhythm in younger adults. The first goal of this application is to understand the mechanism underlying the age-related change in responsiveness of the clock to light. The second goal is to assess whether it is possible to compensate for age-related change in the responsiveness of the aging circadian clock to light by either increasing the intensity of the light exposure or by pharmacological treatment with the calcium channel antagonist nimodipine. The proposed experiments will provide a vast amount of data in which to better understand the effect of age on circadian rhythms and sleep and lead to improved treatments for circadian rhythm and sleep disorders in older adults.

TITLE	TRIAL OF FLUDROCORTISONE FOR CHRONIC FATIGUE SYNDROME
P.I.	ROWE, PETER C.
GRANT NO.	5M01RR000052-410751
Institution:	JOHNS HOPKINS UNIVERSITY

The trial is based on preliminary data showing that upright tilt table testing can provoke a drop in blood pressure consistent with neurally mediated hypotension (NMH) in a high proportion of those with chronic fatigue syndrome (CFS), and that unblinded treatment of the NMH leads to an improvement in CFS symptoms in 40-70% of CFS patients. The specific aim of this study is to determine whether patients aged 18 to 50 years with CFS and NMH will have a greater improvement in (1) self-reported general sense of well being and (2) objective orthostatic tolerance when treated with fludrocortisone than when treated with placebo. Eligible subjects are randomized to receive either fludrocortisone (escalating to 0.1 mg/day) or placebo for nine weeks. In week 8-9 of treatment, subjects undergo repeat tilt testing. The primary outcome measure is the proportion with a 15 point improvement in wellness on a 100 point wellness score, and a secondary outcome is the proportion with improvement in the number of minutes before the development of hypotension during upright tilt.

TITLE	NEURALLY MEDIATED SYNCOPE AND SALT INTAKE LEVELS
P.I.	BLOOMFIELD, DANIEL M.
GRANT NO.	5M01RR000645-310940
Institution:	COLUMBIA UNIVERSITY HEALTH SCIENCES
This abstract is not available.	

TITLE	REGULATION OF ADRENAL FUNCTION IN FIBROMYALGIA
P.I.	ADLER, GAIL K.
GRANT NO.	5M01RR002635-200504
Institution:	BRIGHAM AND WOMEN'S HOSPITAL

The purpose of this study is to characterize the regulation of adrenal steroid hormone production in individuals with fibromyalgia and Chronic Fatigue Syndrome versus healthy individuals.

TITLE	ALDOSTERONE--A CARDIOVASCULAR RISK FACTOR
P.I.	ADLER, GAIL K.
GRANT NO.	5R01HL063423-04
Institution:	BRIGHAM AND WOMEN'S HOSPITAL

Over the past decade, interest in aldosterone as a pathogenic hormone in cardiovascular disease has occurred. In addition to its well-known effect on blood pressure and on sodium (Na+), potassium (K+) and hydrogen (H+) homeostasis, aldosterone is associated with cardiac hypertrophy, fibrosis, nephropathy and strokes. Some of these effects may be secondary to potentiation of the release of plasminogen activator inhibitor, type 1 (PAI-1). Thus, derangement in aldosterone secretion may be an important link between cardiovascular damage and hypertension and heart failure. Angiotensin II (AngII) has several effects similar to aldosterone. Since AngII also regulates aldosterone secretion, the interaction of these two potential cardiovascular risk factors needs to be clarified. The overall goal of this proposal is to test the hypothesis that aldosterone is a cardiovascular risk hormone. The results of these studies will be relevant for several human disease, e.g., congestive heart failure, renal failure, atherosclerosis, and hypertension. To accomplish this overall goal, they will address three groups of specific aims. First, they will establish the principle that aldosterone induces cardiovascular damage and define its extent. They will use three rat models: 1) nitric oxide synthase inhibition with AngII and Na+ supplementation, 2) uninephrectomy with aldosterone and Na+ supplementation, and 3) uninephrectomy with AngII and Na+ supplementation. Preliminary data document that all three models induced cardiovascular damage, and aldosterone is a likely mediator. Second, they will define some of the underlying mechanisms. Two approaches will be used: 1) they will determine the level of Na+ intake required to induce cardiovascular damage, assess if increasing K+ intake is equivalent to blocking aldosterone's effect in inhibiting the damage, and determine the duration of exposure to the experimental paradigm necessary to produce damage. 2) they will assess the role of intermediaries, including tissue AngII, PAI-1, transforming growth factor-beta 1, collagen synthesis, Na+, H+ exchange and Na+, K+ ATPase using cellular and molecular techniques, including mouse knock-out models. Third, they will determine whether established cardiovascular damage can be reversed by modifying aldosterone's action. Their results should better define the rationale for the use of mineralocorticoid antagonists in the prophylaxis of damage to the heart, the kidney and other tissues when aldosterone levels are inappropriately elevated relative to the level of Na+ intake.

TITLE	Mechanisms of Rhinitis in CFS
P.I.	BARANIUK, JAMES N.
GRANT NO.	5R01AI042403-05
Institution:	GEORGETOWN UNIVERSITY

This abstract is not available.

TITLE	CHRONIC LOW BACK PAIN AS A MODEL OF FIBROMYALGIA
P.I.	CLAUW, DANIEL J.
GRANT NO.	5R01AR046049-04
Institution:	GEORGETOWN UNIVERSITY

Fibromyalgia (FM) is defined by a history of widespread pain, and the finding of tender points on examination. Arguably the two most discriminating features of FM are: 1) a generalized disturbance in pain perception, and 2) elevated levels of pro-nociceptive neuropeptides in the cerebrospinal fluid. The first feature, pain induced by a normally non-painful stimuli, is not surprising since this is a defining feature of FM. But it is not certain how tenderness relates to pain, since population based studies have demonstrated that not all persons who are tender have pain, and vice versa. And it has recently become clear that tender points are a poor measure of a person's inherent tenderness. The meaning of these elevated levels of CSF neuropeptides is likewise unclear. These findings may not be specific for FM, and may be the cause of pain and/or tenderness, or may be the result of pain, tenderness, or some other process. Chronic lower back pain (CLBP) is among the most common medical problems in industrial societies. Despite this, little is actually known about the precise cause for most cases of CLBP. Anatomic and psychosocial factors have been demonstrated to predict only a small portion of the variance in the degree of pain or disability in CLBP. In preliminary studies in CLBP, we have demonstrated that tenderness predicts a significant percentage of the variance in both functional status and pain, more than either the severity of path-anatomical abnormality (i.e., X-ray/MRI),or by psychosocial factors. In a small pilot study of a subset of these patients tenderness was correlated with CSF levels of pro-nociceptive neuropeptides. There are 3 specific aims in the proposed study: 1) To confirm in a cross-sectional study of 200 CLBP patients that pain sensitivity predicts more variance in clinical outcome (e.g. functional status, pain level, Roland index) than either anatomic or psychological factors. Furthermore, we will demonstrate that pain sensitivity is an independent trait, and not a surrogate for psychological factors such as depression, anxiety, or work-related stressors. 2) To demonstrate that an individual's global pain sensitivity is determined primarily by physiologic factors (e.g. neurotransmitters in cerebrospinal fluid) and modified by psychosocial factors (e.g. cognitive and behavior influences on pain perception). We will measure the CSF concentrations of pro-nociceptive peptides such as Substance P and Nerve Growth Factor, and hypothesize that the levels of these substances largely determine an individual's global pain sensitivity. This testing will be done in patients with CLBP and FM, as well as sedentary and non-healthcare-seeking controls. 3) To use alternative methods of pain assessment that are much less influenced by psychological factors (e.g., scaling methods, Multiple Random Staircase), using both pressure and thermal stimuli, to examine the true meaning of tender points, and the relationship between these results, and the results of the above noted physiologic and psychologic parameters in individuals with FM and CLBP.

TITLE	RBC MASS, ANS INTEGRITY & SYNCOPE SUSCEPTIBILITY IN CFS
P.I.	HURWITZ, BARRY E
GRANT NO.	5R01HL065668-03
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.

TITLE	EFFECT OF STRESS AND CBSM ON NATURAL KILLER CELL ACTIVITY IN CFS
P.I.	FLETCHER, MARY A.
GRANT NO.	5U01AI045940-040004
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.