2003 NIH Funded CFS Research

NHLBI

TITLE	Transcriptional Regulation of E-Selectin
P.I.	COLLINS, TUCKER O
GRANT NO.	5R01HL045462-14
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.	5R01HL054926-06
Institution	CHILDREN'S HOSPITAL OF PHILADELPHIA

Abstract: *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	MECHANISMS BY WHICH IGF-I STIMULATES SMOOTH MUSCLE CELLS
P.I.	CLEMMONS, DAVID R.
GRANT NO.	5R01HL056850-07
INSTITUTION	UNIVERSITY OF NORTH CAROLINA CHAPEL HILL

ABSTRACT: *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	ORTHOSTATIC INTOLERANCE IN CFS
P.I.	FREEMAN, ROY
GRANT NO.	2R01HL059459-05A1
INSTITUTION	BETH ISRAEL DEACONESS MEDICAL CENTER

ABSTRACT: *The chronic fatigue syndrome (CFS) is a common disorder of unknown cause that incapacitates young individuals in their most productive years. There is evidence that* ***orthostatic*** *intolerance may play a role in the fatigue of patients with CFS. The broad long-term objectives of the project are to delineate the pathophysiology and pathogenesis of* ***orthostatic*** *intolerance in the chronic fatigue syndrome (CFS); to investigate the role of* ***orthostatic*** *intolerance in producing the symptoms of CFS; to use this information to institute physiologically appropriate therapeutic interventions; and thereby decrease the symptoms of fatigue. The Specific Aims of the application are to enhance cardiovagal outflow with low dose atropine and Iosartan and examine the cardiovascular response to* ***orthostatic*** *stress; to characterizing sympathetic nervous transduction to vascular resistance in the lower limbs and characterize the sympathetic responses in the lower limbs to* ***orthostatic*** *stress; to measure transcapillary interstitial fluid filtration during* ***orthostatic*** *stress determine the relationship between capillary filtration and plasma volume; and characterize cerebral blood flow, systemic pressure maintenance, postural tachycardia and parasympathetic outflow. We will assess arterial baroreflex gain by measuring the heart rate and muscle sympathetic nerve activity response to pharmacological provocations; sympathetic transduction by relating muscle sympathetic nerve activity to peripheral resistance; plasma volume using the Evans Blue dye method; venous compliance using venous occlusion plethysmography; and cerebral blood flow velocity with transcranial Doppler. These measures, which comprise the elements of* ***orthostatic*** *tolerance, will be compared with healthy controls selected to match the gender, age and level of physical activity of the subjects. The relationships between these variables and role of covariates such as the level of physical activity and psychiatric state, determined with standardized instruments, will be analyzed using multivariate statistics.*

TITLE	RBC MASS, ANS INTEGRITY & SYNCOPE SUSCEPTIBILITY IN CFS
P.I.	HURWITZ, BARRY E.
GRANT NO.	5R01HL065668-04
INSTITUTION	UNIVERSITY OF MIAMI-MEDICAL

ABSTRACT: *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.	5R01HL066007-03
INSTITUTION	NEW YORK MEDICAL COLLEGE

ABSTRACT: *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.	5R01HL067422-02
INSTITUTION	UNIVERSITY OF TEXAS SW MED CTR/DALLAS

ABSTRACT: *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.	5R01HL070215-02
INSTITUTION	MEDICAL COLLEGE OF GEORGIA

ABSTRACT: *Endothelial cell dysfunction is a primary basis of cardiovascular disease including diabetes mellitus. Evidence suggests 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.*

NINDS

TITLE	Pathophysiology of Neuroimmune Communication
P.I.	QUAN, NING
GRANT NO.	5R01NS040098-03
INSTITUTION	OHIO STATE UNIVERSITY

ABSTRACT: *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.	5R01NS041483-03
INSTITUTION	KAROLINSKA INSTITUTE

ABSTRACT: *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	Clinical Neurocardiology: Catecholamine In Stress & Disease
P.I.	GOLDSTEIN, DAVID S.
GRANT NO.	1Z01NS002979-05
INSTITUTION	

ABSTRACT: *We conducted patient-oriented research in **clinical neurocardiology**. Studies focused on etiology, diagnosis, and pathophysiology of disorders involving catecholamine systems, which use norepinephrine (NE), adrenaline (ADR), or dopamine (DA) as the effector chemicals. The sympathetic nervous system (SNS) regulates cardiovascular function by releasing NE from the nerves as a neurotransmitter. The adrenomedullary hormonal system releases ADR into the bloodstream as a hormone. Loss of DA in a particular brain pathway is known to cause the movement disorder in Parkinson?s disease (PD). Patients were studied who had PD with a fall in blood pressure while standing (orthostatic hypotension, OH); had chronic orthostatic intolerance with tilt-induced loss of consciousness (neurocardiogenic syncope); or had pheochromocytoma, a clinically important tumor that produces catecholamines. Patients with PD+OH all had poor reflexive regulation of the SNS and loss of sympathetic nerves in the heart, confirming PD+OH as not only a movement disorder but also a neurocardiologic disorder. Patients with familial PD from mutation of the gene encoding alpha-synuclein, or from excessive expression of the normal gene, had a loss of cardiac sympathetic nerves. These findings indicate that in PD, both the movement and neurocardiologic disorders reflect synucleinopathy. In contrast, baboons with chronic PD from administration of the neurotoxin, MPTP, had intact cardiac sympathetic innervation. Patients with tilt-induced neurocardiogenic syncope characteristically had antecedent "sympathoadrenal imbalance" (SAI), with high ADR levels and loss of vascular tone in skeletal muscle before the syncope, leading us to propose that SAI may contribute to a positive feedback loop that leads cardiovascular collapse within seconds to minutes. In the diagnostic evaluation of pheochromocytoma, we showed that plasma levels of metanephrines, metabolites of NE and ADR made in the tumor, provide a uniquely and virtually perfectly sensitive screening test. We also completed a large prospective study validating 6-[18F]Fluorodopamine positron-emission tomographic scanning for diagnostic localization of pheochromocytoma. New protocols based on these findings will characterize comprehensively the central neural and autonomic abnormalities in PD+OH and familial PD; assess the efficacy of non-selective beta-adrenoceptor blockade in preventing tilt-induced neurocardiogenic syncope; and relate clinical and neurochemical phenotypes to results of microarray studies of gene expression in human pheochromocytoma tissue.*

NIAID

TITLE	Mechanisms of Rhinitis in CFS
P.I.	BARANIUK, JAMES N.
GRANT NO.	5R01AI042403-06
INSTITUTION	GEORGETOWN UNIVERSITY
ABSTRACT: *This abstract is not available.*	

TITLE	ACTIVITY INTERVENTION FOR CHRONIC FATIGUE SYNDROME
P.I.	JASON, LEONARD
GRANT NO.	5R01AI049720-04
INSTITUTION	DE PAUL UNIVERSITY

ABSTRACT: *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.	5R01AI051270-02
INSTITUTION	UNIVERSITY OF MINNESOTA TWIN CITIES

ABSTRACT: *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.*

TITLE	Sleep and Cytokines in Chronic Fatigue Syndrome
P.I.	NATELSON, BENJAMIN H
GRANT NO.	1R21AI054478-01
INSTITUTION	UNIV OF MED/DENT NJ NEWARK

ABSTRACT: *Chronic fatigue syndrome is a medically unexplained illness. One of the major hypotheses for its cause is immunological dysfunction. Nevertheless, no firm data exist to support the immunological hypothesis. This is likely because prior researchers have ignored the role of **cytokines** in producing restful sleep. Many CFS patients have disrupted sleep, and it is possible that this occurs because of an upregulated network of sleep disrupting **cytokines** in some patients. We propose to measure sleep disrupting **cytokines** (i.e., IL-4 and IL-10) and sleep producing **cytokines** (IL-1beta and TNF-alpha) in CFS patients on their second night in the sleep laboratory (the first night being done to deal with the well known "first night effect" and to eliminate patients with primary sleep disorders or an inability to sleep with instrumentation). In doing these studies, we are aware that there is no "gold standard" to quantify **cytokines**, and so we will use three different approaches - ELISA in plasma, gene message from peripheral blood monocytes (PBM) and ELISPOT to assess PBM function to immunological probes. We will study women only because CFS is predominantly an illness of women, because we want to exclude subjects with primary sleep disorders, which occur mostly in men, and because women have substantially higher levels of **cytokines** than men. We will compare data of CFS patients to those of healthy controls who will be as fatigued as the CFS patients because we will sleep deprive them on the night before the blood sampling night. Moreover, on the blood sampling night, we propose to match the controls to CFS patients for total sleep time. Since some CFS patients sleep without disruption, this design will provide healthy subjects sleeping without disruption and healthy subjects who sleep the same amount as those CFS patients with disrupted sleep. Finally, we will repeat this entire protocol after a day in which subjects perform a maximal exercise test because of the well-known exacerbation of CFS by exertion. We are anticipating that exercise will make some CFS patients sleep even worse than usual and exacerbate an already dysregulated cytokine sleep network.*

NIMH

TITLE	Psychiatric Comorbidity in Chronic Fatigue Syndrome
P.I.	FRIEDBERG, FRED
GRANT NO.	5K23MH001961-03
INSTITUTION	STATE UNIVERSITY NEW YORK STONY BROOK

ABSTRACT: *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.	5R01AR047678-02
INSTITUTION	UNIVERSITY OF WASHINGTON

ABSTRACT: *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.*

TITLE	Role of Fatigue in Rheumatic Diseases
P.I.	LANGE, GUDRUN
GRANT NO.	1U13AR050277-01
INSTITUTION	UNIV OF MED/DENT NJ NEWARK

ABSTRACT: *Fatigue is a common complaint in rheumatic disorders and is one of the strongest predictors of physical dysfunction in patients with Fibromyalgia (FM) and other related disorders, rheumatoid arthritis (RA), osteoarthritis (OA), and systemic lupus erythematosus (SLE). However, research addressing the causes and mechanisms of fatigue is rare in rheumatic illnesses. The lack of scientific evidence focusing on the role of fatigue in rheumatic illness directly impacts on the ability of health care professionals to assess the presence, severity and trajectory of fatigue and to evaluate the relationship of fatigue with other symptoms of these disorders in order to provide appropriate treatment recommendations. Fatigue is one of the most commonly reported, yet least understood and unrelieved symptoms accompanying chronic illnesses. The primary objective of the proposed workshop is to establish a knowledge base of current information on fatigue in rheumatic illness that will be compared with the state of knowledge gained from studies of fatigue in cancer, HIV/AIDS, stroke, and MS. This process will serve to identify knowledge gaps concerning the role of fatigue in rheumatic illness. Directions for future fatigue research in rheumatic illness will be suggested incorporating research methodologies that have proven successful in other somatic disorders. To achieve these objectives, a group of renowned fatigue and sleep researchers drawn from a variety of scientific areas including neuroscience, physiology, immunology, and psychiatry/psychology, clinical practice, as well as representatives of public interest groups will be invited to attend a workshop to be held on March 18 and 19, 2004 at the Dolce Hamilton Park Conference Center in Florham Park, NJ. Presentations addressing definition, conceptualization, and assessment of fatigue in general will proceed state-of-the-art overviews of fatigue research in FM, RA, OA, SLE, cancer, HIV/AIDS, stroke, and MS, and will be followed by concentrated discussions in break-out groups. A position statement summarizing the results from this workshop will be produced at the conclusion of the meeting and disseminated via publication in a peer-reviewed journal. The collaborative and interactive nature of the proposed workshop will ensure that the recommendations generated will have a broad impact on the scientific community, and will generate collaborative, interactive research amongst scientists and clinicians with an interest in rheumatic illnesses.*

NCRR

TITLE	REGULATION OF ADRENAL FUNCTION IN FIBROMYALGIA
P.I.	ADLER, GAIL K.
GRANT NO.	5M01RR002635-190504
INSTITUTION	BRIGHAM AND WOMEN'S HOSPITAL
ABSTRACT: *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	Mechanisms of Rhinitis in CFS
P.I.	BARANIUK, JAMES N.
GRANT NO.	5R01AI042403-06
INSTITUTION	GEORGETOWN UNIVERSITY
ABSTRACT: *This abstract is not available*	

TITLE	RBC MASS, ANS INTEGRITY & SYNCOPE SUSCEPTIBILITY IN CFS
P.I.	HURWITZ, BARRY E
GRANT NO.	5R01HL065668-04
INSTITUTION	UNIVERSITY OF MIAMI-MEDICAL

ABSTRACT: *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.*

NINR

TITLE	ACTIVITY INTERVENTION FOR CHRONIC FATIGUE SYNDROME
P.I.	JASON, LEONARD
GRANT NO.	5R01AI049720-04
INSTITUTION	DE PAUL UNIVERSITY

ABSTRACT: *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.*

OD

TITLE	Chronic Fatigue Syndrome in Adolescents
P.I.	TAYLOR, RENEE R.
GRANT NO.	1R01HD043301-01A1
INSTITUTION	UNIVERSITY OF ILLINOIS AT CHICAGO

ABSTRACT: *In the Senate Labor, Health and Human Services Appropriations Report, it was recommended that researchers explore issues related to the etiology and natural course of chronic fatigue syndrome using longitudinal, repeated-measures designs, with particular attention to pediatric samples. Researchers have documented the development of a fatigue syndrome following mononucleosis in prospective studies of adults. One objective of the proposed investigation is to prospectively study the relationship between infection with mononucleosis and the onset and course of chronic fatigue syndrome over time in adolescents. The following hypotheses will be tested using a prospective, case-control design: (1) Baseline predictors of post-infectious CFS and fatigue severity at 6 months will include greater levels of baseline psychological distress, having a psychiatric diagnosis at baseline, a greater degree of stressful life events at baseline, and higher levels of activity prior to initial infection; (2) Adolescents with CFS, compared with matched controls, will report higher levels of psychological distress, higher rates of psychiatric diagnoses, a greater degree of stressful life events, and lower levels of physical activity following infection at the 6-, 12-, 24- month time points; and (3) Compared with matched controls, adolescents with CFS will demonstrate lower levels of salivary cortisol (peak and trough), reduced natural killer cell function and count, and elevated proinflammatory cytokines at the 6-, 12-, and 24- month time points. At the 6-month time point (clinic visit), adolescents with CFS will also demonstrate higher rates of orthostatic intolerance; and (4) In response to an exercise challenge test at the six-month time point, compared with matched controls, adolescents with CFS will demonstrate lower levels of salivary cortisol and plasma ACTH, and elevated cytokines - illustrating impaired communication between neuroendocrine and immune systems with physical stress. An exploration of the nature and timing of these relationships would provide a preliminary model of etiology and natural course of illness for adolescents with post-viral chronic fatigue syndrome. Results from this investigation may assist physicians in identifying adolescents at high risk for CFS and allow them to initiate preventative measures.*