Chronic Fatigue Syndrome: 2005
Keyword: Chronic Fatigue Syndrome

Title	Chronic Fatigue Syndrome in Adolescents
PI Name	Taylor, Renee R.
Grant Number	5R01HD043301-03
Institution	University Of Illinois at Chicago

Abstract: *DESCRIPTION: 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.*

Title	Orthostatic Intolerance In CFS
PI Name	Freeman, Roy
Grant Number	5R01HL059459-07
Institution	Beth Israel Deaconess Medical Center

Abstract: *DESCRIPTION (provided by applicant): 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	Sleep and Cytokines in Chronic Fatigue Syndrome
PI Name	Natelson, Benjamin H.
Grant Number	5R01AI054478-03
Institution	Univ Of Med/Dent of NJ-NJ Medical School

Abstract: *DESCRIPTION:* ***Chronic fatigue syndrome*** *is a medically unexplained illness. One of the major hypotheses for its cause is immunological dysfunction, but no firm data exist to support the immunological hypothesis. We believe this is because prior researchers have ignored the role of cytokines in producing restful/restless sleep. Many CFS patients have disrupted sleep, and we posit that this occurs because of abnormalities in the pattern of sleep disrupting and sleep producing 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 of plasma levels, gene message in peripheral blood mononuclear cells (PBMC) and ELISPOT to assess PBMC responses 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 that occur mostly in men, and because women have substantially higher levels of cytokines than men. We will exclude women with depression because depression alters sleep and cytokines. We will compare data of CFS patients to those of healthy controls who, on the blood sampling night, will have their total sleep time matched to CFS patients. Since some CFS patients sleep without disruption, we have developed a 2x2 design: CFS vs controls; and sleep disturbed vs normally sleeping. This design will allow us to determine whether CFS, the illness, rather than the disturbed sleep, a symptom of the illness, is responsible for altered cytokine patterns. We will repeat this entire protocol after subjects perform a maximal exercise test and during a night of total sleep deprivation. We anticipate that exercise, which is known to exacerbate CFS symptoms, will worsen an already dysregulated cytokine sleep network while sleep deprivation will also magnify the differences by increasing sleep-producing cytokines in CFS patients without sleep problems and in controls but not in patients with disrupted sleep.*

Title	Psychiatric Comorbidity in Chronic Fatigue Syndrome
PI Name	Friedberg, Fred
Grant Number	5K23MH001961-05
Institution	State University New York Stony Brook

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

Title	Risk Factors Associated with CFS and CF Prognosis
PI Name	Jason, Leonard
Grant Number	1R01AI055735-01A2
Institution	De Paul University

Abstract: *DESCRIPTION:* ***Chronic Fatigue Syndrome*** *(CFS) and* ***chronic fatigue*** *(CF) are severe, disabling conditions. Few studies have examined the natural history course of CFS and* ***chronic fatigue*** *over time, particularly in random, community-based, multi-ethnic populations. In the past, almost all studies with samples of CFS and* ***chronic fatigue*** *patients have relied on referrals from physicians or health facilities, which biased the sample by illness, help-seeking behaviors, or differential access to health are. In contrast, a recent community-based study found the prevalence rate of CFS to be 4% among adults, and the prevalence of CFS among adults was higher among Latino and African-American samples than among the White sample (Jason et al., 1999). These findings might be due to the fact that this sample was collected from an urban area, and a community-based approach was used, thus minimizing the influence of biased data collection procedures. The proposed study will rigorously evaluate the natural history of CFS and* ***chronic fatigue*** *in an ethnically and socioeconomically diverse sample unbiased by illness and help-seeking behaviors, or by differential access to the health care system. Increasingly, the studies suggest that a variety of socio-environmental and psychological risk factors are associated CFS and* ***chronic fatigue*** *maintenance over time. We will perform follow-up on Wave 1 subjects with CFS and* ***chronic fatigue*** *to determine if the associations identified in Wave 1 between CFS and a variety of risk factors will be associated with poorer prognosis in Wave 2. Similar comparisons will be conducted for those with* ***chronic fatigue****. Major benefits of this grant application are the diversity of the population, identification of cases from the community rather than the health care system, and the use of a medical exam to confirm CFS and* ***chronic fatigue*** *diagnoses.*

Title	Rhinitis In Chronic Fatigue Syndrome (CFS)
PI Name	Baraniuk, James N.
Grant Number	1M01RR020359-010020
Institution	Children's Research Institute

There is no text on file for this abstract.

Title	Are Fibromyalgia and Chiari I Malformation Related?
PI Name	Buchwald, Dedra S.
Grant Number	5R01AR047678-04
Institution	University of Washington

Abstract: *DESCRIPTION: 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	Microarrays & Proteomics in MZ Twins Discordant for CFS
PI Name	Sullivan, Patrick F.
Grant Number	5R01AI056014-02
Institution	University of North Carolina Chapel Hill

Abstract: *DESCRIPTION: Despite considerable study,* ***chronic fatigue syndrome*** *(CFS) continues to be both idiopathic and controversial. CFS is associated with considerable morbidity, impairment, and chronicity. Multiple lines of investigation have not yielded widely-accepted and empirically-based hypotheses about its etiology. The goal of this application is to identify biomarkers for CFS, which can also be used to generate hypotheses about the etiology of CFS. The current plan is to correlate microarray and proteomic techniques to biological samples from monozygotic twins who are rigorously discordant for CFS. Discordant monozygotic twins represent an excellent case-control design given their high degree of genetic matching and similarity for many environmental variables and exposure. 28.089 twins from the population-based Swedish Twin Registry have already screened for the symptoms of CFS (funded by NS-41483) and 156 pairs of monozygotic twins, preliminarily discordant for CFS-like illness, have been documented. The application requests funds for clinical evaluation in order to recruit and classify 50 monozygotic twin pairs as rigorously discordant for CFS Zygosity will be proven by genotyping 30 microsatellite markers. Under standardized conditions with careful sample handling, three biological samples can be obtained from consenting twins: total RNA extracted from peripheral blood lymphocytes, peripheral serum, and cerebrospinal fluid. The RNA sample will be analyzed with Affymetrix HG-U133 microarrays that interrogate approximately 45,000 mRNA targets from approximately 33,000 validated human genes. Following removal of high abundance proteins, serum and cerebrospinal fluid samples will be subjected to two-dimensional gel electrophoresis and identification of protein spots of interest via MALDI (aka "proteomics").False discovery rate calculations to show that this design is capable of identifying biomarkers for CFS under many plausible scenarios. Sophisticated statistical, data mining, and bioinformatic techniques will be applied to these data to understand the high dimensionality data generated in these experiments. The team of investigators and consultants assembled for this project has the proven capacity to perform all aspects of this project. This project has the potential to identify biomarkers for CFS and to derive falsifiable hypotheses about its etiology. If successful, this work could lead to profound changes in the understanding of CFS and resolution of some attendant controversies.*

Title	Mechanism of Pain in Patients with Fibromyalgia Syndrome
PI Name	Staud, Roland M.
Grant Number	5R01NS038767-05
Institution	University of Florida

Abstract: DESCRIPTION: Fibromyalgia **syndrome** (FMS) is a symptom based diagnosis that depends on the presence of **chronic** widespread pain and decreased mechanical pain threshold at >= 11 well defined tender points. FMS shows wide overlap with other pain syndromes, including **chronic fatigue syndrome** and irritable bowel **syndrome**. All these disorders share **chronic**, unexplained pain as a clinically relevant symptom and several or all of these syndromes often coexist in an individual patient. Therefore, discovery of FMS pain mechanisms may also benefit patients with related pain syndromes. We have recently shown that FMS patients demonstrate abnormal pain processing, including excessive temporal summation of second pain (windup) and central sensitization. With this application, we will expand our detailed investigation of central/peripheral pain mechanism relevant to FMS pain, using forms of repetitive stimulation that reliably evoke perceptions of second pain. Second pain results from impulse conduction in peripheral C (unmyelinated) afferent axons, and temporal summation of second pain has been shown to result from a central NMDA receptor mechanism within the dorsal horn. The proposed experiments will evaluate peripheral influences on FMS pain and abnormal temporal summation of experimental pain, will describe the central patterns of NMDA receptor activation by nociceptive input, and will compare effects of NMDA antagonists on clinical and experimental pain of female FMS patients and male and female control subjects. Aim 1 will focus on the relationship of clinical pain to abnormal windup (WU) in FMS. Since clinical pain intensities reported for different body areas seem to vary widely within and between FMS patients, we will first test the magnitude of WU and clinical pain ratings in all four body quadrants of FMS patients and then statistically determine the strength of their association. Repetitive thermal and mechanical stimuli will be delivered to FMS patients and normal controls (NC). If clinical pain is indeed related to C-afferent mediated mechanisms we expect to find a positive correlation between WU measurements and clinical pain. Using exercise bouts or ischemic muscle compressions alternating with rest periods, we will characterize the role of musculoskeletal nociceptor input on a) local and generalized pain and b) WU abnormalities of FMS patients (Aim2). We expect to find that muscular activity and associated receptor stimulation will enhance clinical pain both locally and generally. We will test the effects of NMDA receptor antagonists on clinical pain, first pain, second pain, and WU (Aim 3). We will compare the psychophysical test results across pain-free NC and FMS patients in order to ascertain the extent to which abnormalities of NMDA mechanisms contribute to FMS pain with a special focus on FMS related differences. We will use functional brain imaging (fMRI) of temporal summation of second pain in NC and FMS patients to characterize the encoding of brief, repetitive, thermal stimuli in cortical and subcortical structures (Aim 4). We posit that the enhanced WU of FMS patients will strongly correlate with greater neural activation as compared to NC. The proposed experiments will answer important questions about peripheral/central mechanisms of **chronic** pain that are relevant to the diagnosis and treatment of FMS. In addition, our findings may contribute to the understanding of pain mechanisms related to other **chronic** pain disorders.

Title	Neural Circuitry Underlying Chronic Stress Effects
PI Name	Bhatnagar, Seema
Grant Number	5R01MH067651-03
Institution	University Of Michigan at Ann Arbor

Abstract: *DESCRIPTION (provided by applicant):* ***Chronic*** *exposure to stress in the form of major adverse life events is associated with the development of disorders such as depression, anxiety and post-traumatic stress disorder and* ***chronic fatigue syndrome****. Changes in activity within the hypothalamic-pituitary-adrenal (HPA) axis are important features of these disorders and likely reflect plasticity in brain circuitry that coordinates these neuroendocrine responses with behavioral and autonomic function. Animals undergoing* ***chronic*** *stress exhibit many of the neuroendocrine autonomic and behavioral changes seen in individuals with disease. Using HPA activity as our primary endpoint, we have identified the posterior division of the paraventricular nucleus of the thalamus (pPVTh) as a critical mediator of HPA responses in chronically stressed rats though it does not seem to be functionally active in rats exposed to acute stress. Therefore, the pPVTh seems to control HPA activity specifically within the context of prior stress experience. In this proposal, we seek to characterize the neural circuits that mediate the primarily inhibitory effects of the pPVTh on HPA activity. The efferent projections of the pPVTh are limited and are primarily to limbic structures including the amygdala, prefrontal cortex and bed nucleus of the stria terminalis but also to a hypothalamic region that can more directly control HPA activity. Our general hypothesis is that the pPVTh exerts its influence through changing activity in limbic structures but not hypothalamic structures since limbic regions are more capable of evaluating sensory information within the context of past stress history. More specifically, we will determine whether the pPVTh can exert its inhibitory influence on HPA activity by acting on limbic GABA-ergic systems (Aim 1) and/or by serving as a site of negative feedback effects of glucocorticoids released by the* ***chronic*** *stress exposure (Aim 2). Aim 3 focuses on the pathways through which cholecystokinin released within the pPVTh alters HPA activity specifically in chronically stressed rats and Aim 4 will examine how central CRF systems interact with the pPVTh and its associated limbic circuitry. Given the specificity of pPVTh effects to the* ***chronic*** *stress state, characterizing this pPVTh-limbic circuitry is fundamental to understanding the association between* ***chronic*** *stress and changes in physiology and behavior that can lead to disease.*

Title	Neural Circuitry Underlying Chronic Stress Effects
PI Name	Bhatnagar, Seema
Grant Number	7R01MH067651-04
Institution	Children's Hospital of Philadelphia

Abstract: *DESCRIPTION (provided by applicant):* ***Chronic*** *exposure to stress in the form of major adverse life events is associated with the development of disorders such as depression, anxiety and post-traumatic stress disorder and* ***chronic fatigue syndrome****. Changes in activity within the hypothalamic-pituitary-adrenal (HPA) axis are important features of these disorders and likely reflect plasticity in brain circuitry that coordinates these neuroendocrine responses with behavioral and autonomic function. Animals undergoing* ***chronic*** *stress exhibit many of the neuroendocrine autonomic and behavioral changes seen in individuals with disease. Using HPA activity as our primary endpoint, we have identified the posterior division of the paraventricular nucleus of the thalamus (pPVTh) as a critical mediator of HPA responses in chronically stressed rats though it does not seem to be functionally active in rats exposed to acute stress. Therefore, the pPVTh seems to control HPA activity specifically within the context of prior stress experience. In this proposal, we seek to characterize the neural circuits that mediate the primarily inhibitory effects of the pPVTh on HPA activity. The efferent projections of the pPVTh are limited and are primarily to limbic structures including the amygdala, prefrontal cortex and bed nucleus of the stria terminalis but also to a hypothalamic region that can more directly control HPA activity. Our general hypothesis is that the pPVTh exerts its influence through changing activity in limbic structures but not hypothalamic structures since limbic regions are more capable of evaluating sensory information within the context of past stress history. More specifically, we will determine whether the pPVTh can exert its inhibitory influence on HPA activity by acting on limbic GABA-ergic systems (Aim 1) and/or by serving as a site of negative feedback effects of glucocorticoids released by the* ***chronic*** *stress exposure (Aim 2). Aim 3 focuses on the pathways through which cholecystokinin released within the pPVTh alters HPA activity specifically in chronically stressed rats and Aim 4 will examine how central CRF systems interact with the pPVTh and its associated limbic circuitry. Given the specificity of pPVTh effects to the* ***chronic*** *stress state, characterizing this pPVTh-limbic circuitry is fundamental to understanding the association between* ***chronic*** *stress and changes in physiology and behavior that can lead to disease.*

Title	Pacific Research Center for Marine Biomedicine
PI Name	Laws, Edward A.
Grant Number	5P50ES012740-02
Institution	University Of Hawaii At Manoa

Abstract: *DESCRIPTION (provided by applicant) The proposed work builds on the University of Hawaii 's research strengths in oceanography and tropical medicine and its location in the center of the largest ocean on Earth to create a Pacific Research Center for Marine Biomedicine (PRCMB). Through the collaboration of an interactive milieu of oceanographers and medical researchers, the PRCMB will conduct hypothesis-driven, interdisciplinary research on harmful algal blooms (HAB), water-and vector-borne diseases, and marine-derived pharmaceuticals and probes, in the thematic context of tropical coastal waters and small islands. HAB research will focus on the ciguatera problem, which is unique to the tropics. Specific goals of the research will include (1) a better understanding of the ecology of Gambierdiscus toxicus, with the expectation of identifying management strategies for reducing the frequency of outbreaks, (2) the development of inexpensive, broadly applicable, and rapid methods for testing for the presence of the ciguatoxin in fish, and (3) the development of methods to measure low concentrations of the toxin in humans, with the expectation of determining whether* ***chronic*** *exposure to ciguatoxin may be associated with enigmatic health conditions, such as* ***chronic fatigue syndrome****. Research relevant to water-borne pathogens will explore the feasibility of determining human health risks associated with water contact through the direct detection of pathogens in two ways: (1) the use of molecular biological methods to determine the presence, viability, and virulence of a subset of enteric pathogens with the expectation of developing a practical water quality testing protocol based on molecular biological methods and (2) the use of marine bivalves as natural concentrators and sequesters of pathogens with the expectation that the concentration of certain pathogens in bivalves may prove to be a useful diagnostic tool in water quality monitoring. The marine pharmaceutical project will take advantage of recent advances in microbial isolation and culturing methods and the unique and largely unexplored tropical microbial flora surrounding the Hawaiian Islands to (1) isolate and culture marine micro-organisms from tropical coastal and open ocean seas, (2) screen these organisms for the production of antibiotics and other pharmaceuticals with potential public health applications, particularly the treatment of neurodegenerative, cardiovascular, and infectious diseases, and (3) develop molecular genetic tools for the isolation and expression of relevant biosynthetic genes and for expression of pathways in host organisms for the production of marine pharmaceuticals. These research programs will be supported by a core microbial culture and characterization facility that will provide microbial biomass for screening and the isolation of secondary metabolites, develop new enrichment culture isolation techniques, provide and maintain analytical facilities (GC/MS and LC/MS/MS) for PRCMB scientists, and engage faculty from other disciplines in collaborative work with Center investigators. A Pilot Project Program will*

carry out exploratory research that complements major projects or addresses gaps in the scientific agenda of the PRCMB.

Title	The Neural Immune Mechanisms and Genetic Influences on C
PI Name	Stratton, Pamela
Grant Number	1Z01HD008769-02
Institution	National Institute of Child Health and Human Development

Abstract: Chronic *pelvic pain accounts for 10 percent of all gynecology visits and is a significant problem for thousands of women. Most women with* ***chronic*** *pelvic pain have endometriosis. To determine the possible contribution of pelvic adhesions in women with pelvic pain, we evaluated adhesion reformation following laparoscopic excision of endometriosis and adhesiolysis in women with* ***chronic*** *pelvic pain in 38 women who had two surgeries. Adhesions, or adhesions combined with endometriotic lesions, were significantly more likely to reform at second surgery compared to sites having only an endometriosis lesion. Thick adhesions were associated with a significantly increased likelihood of adhesion reformation, compared to thin adhesions. Endometriotic lesions or adhesions involving the ovary were more likely to be associated with adhesions at a subsequent surgery, compared to lesions in the adjacent ovarian fossa or fallopian tube. Most patients developed adhesions after radical surgical excision of endometriosis for pelvic pain. The high incidence of adhesion formation following surgery for endometriosis underscores the importance of optimizing surgical techniques to potentially reduce adhesion formation. In order to better understand endometriosis,* ***chronic*** *pelvic pain and their co-morbidities, we analyzed a survey of almost 4000 women with surgically diagnosed endometriosis conducted by the Endometriosis Association. Almost all responders had pain (99%), and many reported infertility (41%). In this cohort of women with endometriosis, hypothyroidism, fibromyalgia,* ***chronic fatigue syndrome****, autoimmune diseases, allergies, and asthma were all significantly more common than in women in the general U.S. population. In the coming year, we plan to conduct a more in depth analysis of women with endometriosis to assess the diagnostic process and utilization and effectiveness of treatments, to estimate the prevalence of co-morbid diseases including cancers, endocrine diseases, and infections, and to evaluate the reproductive and gynecologic health of women who responded to the survey.*

Title	Viral dsRNA as a Mediator of Chronic Muscle Diseases
PI Name	Tam, Patricia E.
Grant Number	5R01AI051270-04
Institution	University of Minnesota Twin Cities

Abstract: *DESCRIPTION (provided by applicant): 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	Neural Substrates of Arousal and Emotion
PI Name	Jacobs, Barry L.
Grant Number	5R01MH023433-32
Institution	Princeton University

Abstract: *DESCRIPTION (provided by applicant): Serotonin, acting as a chemical neurotransmitter in the central nervous system (CNS), is importantly implicated in a variety of human neuro- and psychopathologies. However, its basic neurobiological role remains somewhat obscure. A true appreciation of how serotonin functions in disease processes, and treatment of them, presupposes an understanding of its actions in normal mammalian physiology and behavior. To that end, the present research is aimed at furthering knowledge of the basic functioning of the CNS serotonin system primarily through recording the electrical activity of brain serotonin neurons in behaving animals. Recordings will be made in both the rostral/ascending group of serotonin neurons (in the dorsal raphe nucleus) as well as the caudal/descending group (in the nuclei raphe obscurus and pallidus). The proposed studies are an outgrowth of our basic hypothesis that the activity of serotonin neurons is closely linked to level of behavioral activation/tonic motor activity, and especially to repetitive motor activity (central pattern generator-mediated). Two major groups of experiments are proposed: 1) environmental and behavioral factors that may modulate the basic activity of these brain cells, and the neurochemicals that mediate these effects; 2) the role of brain serotonin neurons in central* ***fatigue****. The importance of this latter issue derives from the fact that* ***fatigue*** *is considered an important component in a number of disease processes (e.g.,* ***chronic fatigue syndrome****, multiple sclerosis, and depression). In addition to single unit recordings in behaving animals, the experiments will employ: 1) In vivo microdialysis measures of brain serotonin and dopamine; 2) Local drug administration by means of reverse microdialysis; 3) c-Fos expression (in conjunction with double labeling) as an indicator of serotonin neurons activated under specific conditions; and 4) Computer-generated spike train analyses.*

Title	Neurodegenerative Effects of Botulinum Toxins
PI Name	Lipton, Stuart A.
Grant Number	5P01AI055789-020003
Institution	Burnham Institute for Medical Research

Abstract: *Botulinum toxins (BoNTs) are among the most potent toxins known, thus defining it as a Class A bio-terrorism threat by NIAID. Intoxication with BoNT leads to flaccid paralysis, respiratory arrest, and death by blocking acetylcholine release at neuromuscular junctions. BoNTs mediate paralysis by cleaving molecules found in synaptic terminals, synaptosomal-associated protein of 25 kD (SNAP-25), vesicle-associated membrane protein (VAMP), or syntaxin. Early treatment with humanized antibodies can prevent progression and death by BoNT intoxication. However, many surviving patients exhibit a persistent or* ***chronic fatigue syndrome****. Unfortunately, not much is known about the cellular and molecular mechanism of this* ***fatigue syndrome****. A prime hypothesis here is that this disabling* ***fatigue syndrome*** *is caused by cell injury and death of motoneurons and that different BoNT serotypes have differential effects in mediating this newly recognized neurodegenerative disorder. Thus the goal of this project will be to gain new insight into how BoNTs mediate motoneuron cell death. To achieve this goal, primary motoneurons will be analyzed using approaches such as cell biology, immunocytochemistry, time-lapse deconvolution microscopy, electron microscopy, and gene and peptide transfer. Among the specific questions that will be addressed are: (1) How does BoNT/C but not BoNT/A induce damage to synaptic endings and neurites, eventually resulting in motoneuron degeneration? (2) What are the real-time changes in synaptic endings and neurites, cytoskeleton, and mitochondria linked to BoNT-induced motoneuron cell death? (3) Does cleavage of SNAP-25, syntaxin, or synaptobrevin/VAMP suffice to induce motoneuron damage and cell death initiated by BoNTs? Results obtained here will in general lead to a better understanding of the mode of action of BoNTs. Most importantly, new insights gained here will set the foundation to treat and prevent long-term, devastating neurological effects linked to BoNT-mediated intoxication after a bioterrorism attack.*