Chronic Fatigue Syndrome: 2004
Keyword: Chronic Fatigue Syndrome

TITLE	Chronic Fatigue Syndrome in Adolescents
P.I.	TAYLOR, RENEE R.
GRANT NO.	5R01HD043301-02
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
P.I.	FREEMAN, ROY
GRANT NO.	5R01HL059459-06
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
P.I.	NATELSON, BENJAMIN H.
GRANT NO.	2R01AI054478-02
Institution:	UNIV OF MED/DENT NJ NEWARK

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
P.I.	FRIEDBERG, FRED
GRANT NO.	5K23MH001961-04
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	Circulatory Dysfunction in Chronic Fatigue Syndrome
P.I.	STEWART, JULIAN M
GRANT NO.	5R01HL066007-04
Institution:	NEW YORK MEDICAL COLLEGE

Abstract: *DESCRIPTION:* ***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	Are Fibromyalgia and Chiari I Malformation Related?
P.I.	BUCHWALD, DEDRA S.
GRANT NO.	5R01AR047678-03
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	ACTIVITY INTERVENTION FOR CHRONIC FATIGUE SYNDROME
P.I.	JASON, LEONARD
GRANT NO.	5R01AI049720-05
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	CHRONIC FATIGUE SYNDROME
P.I.	MCCULLY, KEVIN K.
GRANT NO.	3P41RR002305-20S10099
Institution:	UNIVERSITY OF PENNSYLVANIA

Abstract: *ABSTRACT NOT PROVIDED*

TITLE	Effect of Parental Chronic Fatigue Syndrome on Offspring
P.I.	SMITH, MARK H.
GRANT NO.	2M01RR000037-440827
Institution:	UNIVERSITY OF WASHINGTON

Abstract:
There is no text on file for this abstract.

TITLE	Microarrays & Proteomics in MZ Twins Discordant for CFS
P.I.	SULLIVAN, PATRICK F.
GRANT NO.	1R01AI056014-01A1
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
P.I.	STAUD, ROLAND M.
GRANT NO.	2R01NS038767-04A2
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	Subject Registry: Interdisciplinary Studies of Chronic Multi-Symptom Illnesses
P.I.	WILLIAMS, DAVID A.
GRANT NO.	5M01RR000042-441413
Institution:	UNIVERSITY OF MICHIGAN AT ANN ARBOR

Abstract:
There is no text on file for this abstract.

TITLE	Neural Circuitry Underlying Chronic Stress Effects
P.I.	BHATNAGAR, SEEMA
GRANT NO.	5R01MH067651-02
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	Maximizing Beneficial Exercise Effects in Fibromyalgia.
P.I.	JONES, KIM D.
GRANT NO.	5R01NR008150-03
Institution:	OREGON HEALTH & SCIENCE UNIVERSITY

Abstract: *DESCRIPTION: (provided by applicant) Fibromyalgia (FM) is a common, costly and debilitating* ***chronic*** *pain* ***syndrome*** *diagnosed in nearly 6 million Americans, 90% of whom are women. Conservative estimates place direct and indirect costs of FM at $700 million annually. By definition, people with FM have* ***chronic*** *widespread pain and specified tender point areas. Other symptoms associated with FM include disrupted sleep,* ***fatigue****, decreased cognition, visceral and other pain syndromes, neurological symptoms, post-exertion muscle pain and exercise intolerance. The majority of people with FM are known to be aerobically unfit, have poor muscle strength and limited flexibility. Deconditioned muscle is theoretically more prone to muscle microtrauma, which causes localized pain and triggers widespread pain through disordered central nervous system processing (i.e., central sensitization). A negative cycle of de-conditioning occurs in FM in large part due to exercise-induced pain that limits exercise tolerance. Dysfunction of the hypothalamic-somatotropic axis, specifically growth hormone (GH)/insulin-like growth factor-one (IGF-1), may also contribute to exercise induced pain and exercise intolerance in FM, due to the critical role of GH/IGF-1 in muscle homeostasis and repair following exercise. Over the past 25 years, the broad research theme of the Oregon Health and Science University's (OHSU) Fibromyalgia Research and Treatment Team has been investigating pain in fibromyalgia with an emphasis on exercise and pharmacological therapies. We recently documented GH/IGF-1 dysfunction in persons with FM at rest, and in response to exercise. We also pharmacologically altered the GH/IGF-1 axis in women with FM, with resultant improvements in pain and exercise tolerance by self-report. The focus of the proposed study is to test the effects of exercise training in women with FM whose GH profiles have been experimentally manipulated with low dose pyridostigmine bromide (Mestinon). To fully investigate the effects of exercise training and pyridostigmine bromide, a 2 x 2 x 2 (exercise x drug x time) design will be used. We propose a randomized clinical trial in which four groups of participants are observed over time (placebo only, pyridostigmine bromide only, exercise + placebo and exercise + pyridostigmine bromide). We will test the effects of the exercise and drug independent variables, alone and in combination, on the outcome variables of 1) pain and 2) FM associated symptoms and impact, cognition and quality of life. The specific aims of this study are to: Test the effects of a 6-month, 3-times-weekly exercise training program plus 3-times-daily 60 mg pyridostigmine bromide on pain, the primary and defining symptom of FM; and test the effects of a 6-month, 3-times-weekly exercise training program plus 3-times-daily 60 mg pyridostigmine bromide on FM-associated symptoms and impact, cognition, and quality of life.*

TITLE	Pacific Research Center for Marine Biomedicine
P.I.	LAWS, EDWARD A.
GRANT NO.	1P50ES012740-01
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	SEX HORMONES, STRESS, AND PAIN IN FIBROMYALGIA
P.I.	OKIFUJI, AKIKO
GRANT NO.	5R01AR046303-06
Institution:	UNIVERSITY OF UTAH

Abstract: *Many* ***chronic*** *pain disorders are more prevalent in women. Women also exhibit greater sensitivity to experimentally induced pain. Research has suggested that sex hormones exert multiple impacts upon human CNS, including the sympathoadrenal and serotonergic functions. The primary purpose of this proposal is to test several components of a conceptual model hypothesizing how the hormonal and stress factors are related to fibromyalgia* ***syndrome*** *(FMS), a* ***chronic*** *musculoskeletal pain disorder, predominantly seen in women. We will use both laboratory and field study approaches to evaluate the effects of sex hormones in pain sensitivity, stress reactivity, and symptom perception across a menstrual cycle in women with FMS, in comparisons to healthy pain-free females (PFF) and males (PFM). Specifically, we will test sex steroid production in FMS, estrogenic effects on the sympathoadrenal functions in response to stressors, estrogenic effects on pain sensitivity, involvement of sex hormones in perimenstrual and FMS symptoms across menstrual cycle, and sleep and stress as predictors of pain,* ***fatigue****, distressed mood in FMS. A total of 300 subjects (100 each in FMS, PFF, PFM) will undergo home urine tests, daily symptom monitoring, blood and saliva sampling, and experimentally induced stress and pain testing. The laboratory testing will be repeated on 3 separate days: once during the mid-luteal phase (high estrogen E + high progesterone P), once during the perimenstrual phase (low E + low P), and once during the late-follicular phase (high E + low P). Male subjects will be scheduled using a "yoked-cycle" to female subjects. Each subject will be randomly assigned to one of the two experimental conditions ("stress-priming" vs "non-stress- priming" tasks just prior to pain testing). Blood pressure and salivary cortisol will be sampled multiple times throughout the laboratory sessions. The findings from this project are expected to promote better understanding of the role of female sex hormones in noxious sensory processing in* ***chronic*** *pain disorders.*

TITLE	Chronic Pelvic Pain: Genetics/Neural Immune Mechanisms
P.I.	STRATTON, PAMELA
GRANT NO.	1Z01HD008769-01
Institution:	Not Available

Abstract: Chronic *pelvic pain associated with endometriosis is poorly understood. This study is an effort to better understand pelvic pain and identify novel medical approaches for understanding it and treating it. We will examine the relations among sex hormones, pain processing, immune system substances and pain related genes. We will also examine changes in levels of hormonal and immune substances in the blood, endometriosis lesions and normal endometrial tissue. Myofascial pain has been noted in women with endometriosis and* ***chronic*** *pelvic pain. We will study how the nerve, muscle and skeletal systems are involved in pelvic pain by performing an in depth pain assessment. Finally, stress plays an important role generating and perpetuating* ***chronic*** *pain. We will examine how the hormones related to the stress response may be altered in pelvic pain. Comorbidities of endometriosis including autoimmune and other disease states. 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 are all significantly more common than in women in the general U.S. population. In the next two years, we are going to analyze the remainder of the survey to examine the types of medical and surgical treatments these women have experienced and their effectiveness, as well as other co-morbidities.*

TITLE	Viral dsRNA as a Mediator of Chronic Muscle Diseases
P.I.	TAM, PATRICIA E.
GRANT NO.	5R01AI051270-03
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	Mechanisms of Rhinitis in CFS
P.I.	BARANIUK, JAMES N.
GRANT NO.	5R01AI042403-07
Institution:	GEORGETOWN UNIVERSITY
Abstract: *This abstract is not available.*	

TITLE	Use of viagra to Alter Symptoms in Pts with CFS
P.I.	FRIEDMAN, THEODORE C.
GRANT NO.	5P20RR011145-100002
Institution:	CHARLES R. DREW UNIVERSITY OF MED & SCI
Abstract: *There is no text on file for this abstract.*	

TITLE	International Symposium on Motor Control Using TMS
P.I.	HORTOBAGYI, TIBOR
GRANT NO.	1R13NS047105-01
Institution:	EAST CAROLINA UNIVERSITY

Abstract: *DESCRIPTION (provided by applicant): This application is a single-year request of support for an international symposium, "Mechanisms of Movement and Sensation Using Transcranial Magnetic Stimulation" (TMS) as part of the XVth biennial Congress of the International Society of Electrophysiology and Kinesiology (ISEK), Boston, June 18-21, 2004. The rationale for the symposium is that in this era of specialization, research subdisciplines on the one hand and basic researchers and therapists on the other, tend to separate. This symposium is an effort to minimize this separation. The symposium's aim is to generate a novel synthesis of basic science and clinical mechanisms of motor cortex plasticity and thus facilitate the design of rehabilitation programs. Pascual-Leone, co-chair, (US), will provide a historical perspective on TMS and rTMS. Valero Cabre (US) will discuss the effects of TMS and rTMS on the basic electrophysiological and metabolic properties of cortical neurons with reference to Parkinson's disease. Hortobagyi (US) will discuss the contralateral organization of the human nervous system. Taylor (Australia) will address the mechanisms of central* ***fatigue*** *in polio and* ***chronic fatigue syndrome****. Sawaki (US) will present on training dependent plasticity of the motor cortex as evidence for short-term motor memory, specifically in stroke. Rothwell (UK) will address the effect of afferent input on motor cortex organization and plasticity in healthy subjects and in patients with dystonia and hand cramps. Manto (Belgium) as co-chair will moderate the discussions. The symposium will provide maximal interaction between speakers and attendees as it will take place in a plenary session format as the only ongoing session. Through student discounts, it will provide an economical opportunity for biomedical trainees to attend. The presentations will be published in IEEE Engineering in Medicine and Biology, making a substantial impact on the field by attracting the interest of neurologists, clinical neurophysiologists, basic and clinical movement and sensation neuroscientists, physical therapists, biomechanists, biomedical engineering researchers, roboticists, educators and students from the US and abroad.*

TITLE	Neural Substrates of Arousal and Emotion
P.I.	JACOBS, BARRY L.
GRANT NO.	5R01MH023433-31
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	Pathogenesis and treatment studies in patients with NOMI
P.I.	LIPSKY, PETER E.
GRANT NO.	1Z01AR041138-02
Institution:	Not Available

Abstract: *Summary: 1) BACKGROUND These studies investigate the impact of IL-1 blockade on a number of autoinflammatory diseases: NOMID, an acronym for "Neonatal Onset Multisystem Inflammatory Disease", is a rare* ***chronic****, systemic inflammatory disease leading to major disability in affected individuals. Affected patients present with an urticarial rash, fever, aseptic meningitis, papilledema, high frequency, sensorineural hearing loss, bony overgrowth especially of the knees, growth retardation and a significant number of patients are cognitively impaired. NOMID presents at the most severe end of a spectrum of diseases that are associated with mutations in CIAS1, a gene located on chromosome 1. The other two diseases being familial cold induced autoinflammatory* ***syndrome*** *(FCAS) or Muckle Wells* ***syndrome*** *(MWS). In contrast to FCAS and MWS, mutations in NOMD patients occur spontaneously and are present in about 50% of the patients. When we and one other group discovered that spontaneous missense mutations in the NACHT domain of CIAS1 are the cause of NOMID, the pathophysiological pathways associated with molecules containing the pyrin domain were just being associated with up regulation of caspase-1 or IL-1 converting enzyme (ICE) which, leads to increased cleavage of a pro-form of IL-1 into its active component. We subsequently hypothesized that IL-1 blockade may lead to clinical improvement in children with NOMID. A clinical trial using the IL-1 receptor antagonist Anakinra is currently conducted in children with NOMID. The other inflammatory conditions we study are as follows: FCAS is associated with a cold induced urticarial rash. In addition to the development of signs and symptoms of systemic inflammation, such as elevation of acute phase reactants, fever, joint pain,* ***fatigue*** *accompany the rash and resolves several hours after the cold exposure subsides. MWS is associated with a persistent urticarial rash that can not clearly be linked to a cold stimulus, the development of high frequency hearing loss, in some cases papilledema, and the development of amyloidosis. Still's disease is a rare arthritic* ***syndrome*** *without currently identified genetic associations. Still's disease presents with spiking fevers, evanescent salmon colored rash, arthritis, arthralgia and hepatosplenomegaly. Although Still?s disease typically first occurs during childhood, it can also have its onset in adulthood. FMF is a recessively inherited disease with a defect in the FMF gene that encodes for an abnormal protein called pyrin. FMF is characterized by episodes of fever, serositis, arthritis and in rare cases patients develop amyloidosis. This disease has been extensively been studied in Dr Daniel Kastner?s laboratory. Those projects are conducted in collaboration with his group. The gene that is mutated in the CIAS1 associated diseases encodes a protein, cryopyrin that has similarities in structure and function with pyrin the protein mutated in FMF. Both mutated proteins are associated with up-regulation of IL-1 production in vitro and in vivo. This has formed the rationale to develop a treatment approach targeting the IL-1 pathway as outlined above. 2) OBJECTIVE OF PRESENT STUDIES: a. the first study conducted in children and adults with NOMID evaluates the impact of IL-1 blockade with the FDA approved IL-1 receptor antagonist anakinra on the clinical signs and symptoms and laboratory markers of inflammation. Anakinra is given daily by subcutaneous injections. This study has completed recruitment. b. a second study is imitated to evaluate the impact of a new therapeutic agent, IL-1 TRAP with a longer halflife than anakinra on the clinical signs and symptoms and laboratory measures of inflammation in adult patients with CIAS1 diseases (NOMID, MWS or FCAS) and to test the impact of IL-1blockade in two other inflammatory diseases (adult onset Still?s disease and colchizine resistant, mutation proven FMF 3) RESULTS DURING THE PAST YEAR AND ONGOING INITIATIVES a. The anakinra study completed recruitment. All 18 patients had remarkable clinical and laboratory responses to anakinra. In 15 of those patients laboratory markers of inflammation (including the erythrocyte sedimentation rate, the C reactive protein and the serum amyloid A protein level) completely normalized and clinical signs and symptoms disappeared or improved markedly. During a flare period when drug was withheld, all 11 patients who underwent this flare period developed rash, joint pain, headaches fevers and other clinical signs and symptoms that were present before their disease was treated with anakinra. In all patients laboratory markers of inflammation increased significantly during the flare period. Reinstitution of therapy produced the same immediate responses to anakinra as was seen with the first administration. b. The protocol to conduct the IL-1 TRAP study was approved by the regulatory agencies and the initiation of recruitment is imminent. 4) CONCLUSIONS AND SIGNIFICANCE a. As we hypothesized in the anakinra trial, IL-1 overproduction/activation as a result of de novo mutations in CIAS1 in children with NOMID seem to be the major pathophysiologic pathway promoting inflammation in children with NOMID. Blockade of IL-1 with the IL-1 receptor antagonist anakinra produces effective, almost instant relief from the clinical signs and symptoms. In addition ocular and auditory signs and symptoms have stabilized over the period of observation. We also have evidence that a number of the CNS manifestations of the disease (hearing loss, vision loss due to optic nerve edema and optic nerve atrophy and leptomeningitis) are inflammatory in nature. If long term IL-1 blockade will prevent progression or even prevent the development of those symptoms needs to be tested in longer term studies. b. The IL-1 TRAP study will show if a new agent blocking the effect of IL-1, that can be administered weekly will also have a major impact on treating patients with NOMID. Subsequently, administration of IL-1 TRAP to patients with two other autoinflammatory diseases, adult Still?s disease and FMF will delineate the impact of IL-1 blockade in these patients and may possibly point us to the important pathopysiologic pathways leading to disease expression in both diseases.*

TITLE	Effects of Corticotropin-Releasing Hormone Infusion
P.I.	PAPANICOLAOU, DIMITRIS A.
GRANT NO.	5M01RR000039-440620
Institution:	EMORY UNIVERSITY
Abstract: *There is no text on file for this abstract.*	

TITLE	Disordered Responses to Orthostatic Stress in ... Gulf War Syndrome Symptoms
P.I.	ROWE, PETER C.
GRANT NO.	5M01RR000052-430836
Institution:	JOHNS HOPKINS UNIVERSITY
Abstract: *There is no text on file for this abstract.*	