FY 2001 ORWH-SUPPORTED RESEARCH INITIATIVES

AGING

TITLE: **Age Difference of Spouses and Long-Term Care** **NIA**
P.I.: **Darius Lakdawalla, Ph.D.**
INSTITUTION: **RAND, Santa Monica, CA**
GRANT NO.: **1R03AG19900-01**
KEYWORDS: **nursing home use, long-term care, aging, spousal support, widowhood, caregiving**
TYPE STUDY: **Basic**
AMOUNT: **$86,538**

The magnitude of long-term care expenditures, $100 billion annually, makes it imperative for us to understand past and future trends in long-term care demand. The aim of the proposed research is to examine how the declining age gap between spouses will affect future trends in the demand for long-term care. It has been well-established that the presence or absence of a healthy spouse is a major determinant of nursing home entrance: a disabled person married to a healthy spouse is about half as likely to enter a nursing home as a disabled person without a health spouse. In turn, the availability of healthy spouses may have been substantially affected by the shrinking age gap between spouses over the twentieth century. A woman born in 1900 on average ended up with a husband who was 4.2 years older than she. The same woman born in 1950, however, would have ended up with a husband just 2.5 years older. The investigators propose to show that this decline has two effects: (1) All elderly couples will tend to stay married longer, because they are more closely matched in age; and (2) Today's elderly women will tend to have younger, healthier husbands, but today's elderly men will tend to have older wives. The first effect will reduce nursing home demand, while the second has an ambiguous effect. The investigators propose to quantify both effects and estimate their overall effect on nursing home demand. Life table data from the Social Security Administration will be used to compute the effect of the changing age gap on the prevalence of marriage among the elderly. Data from the AHEAD study will be used to estimate the probability of nursing home entrance by disability, marital status, and the age of a married person's spouse. As part of this analysis, Census data will be utilized to impute data on the ages of deceased spouses absent from the AHEAD. This analysis quantifies the effect of the changing age gap of the probability of nursing home entrance for married people. Using estimates of the changing probability of being married, and the changing probability of nursing home entrance for married people, the total effect of the changing age gap on overall nursing home demand will be computed.

TITLE: **A Fall Prevention Program for High Risk Elderly Women** **NINR**
P.I.: **Jean F. Wyman, Ph.D., R.N.**
INSTITUTION: **University of Minnesota, Minneapolis, MN**
GRANT NO.: **5R01NR005107-02**
KEYWORDS: **injury prevention, nursing intervention, clinical research, aging**
TYPE STUDY: **Clinical**
AMOUNT: **$150,000**

The long term objective of this study is to develop cost-effective, community-based strategies for the prevention of falls in high risk elderly women. Specific aims: 1) Test the efficacy of a fall prevention program for high risk elderly women on fall rates over one and two years; 2) Determine the effects of the fall prevention program on postural competence, functional performance, and a variety of other outcome measures; and 3) Identify demographic, clinical, personal, functional, and postural competence variables that predict long-term exercise adherence for participants in the fall prevention program. The participants will be 250 community-dwelling women who are aged 70 and over, mentally intact, ambulatory, with postural instability and at least one other fall risk factor, not currently involved in regular exercise, and medically stable with physician approval for independent exercise participation. This study will provide information on the efficacy and cost of simple interventions designed to prevent falls and fall-related injuries, reduce preclinical disability, maintain long-term exercise adherence, and improve quality of life for older women.

ADOLESCENT HEALTH

TITLE: The National Study of Adolescent Health - ADD Health — **NICHD**
P.I.: Richard Udry, Ph.D.
INSTITUTION: University of North Carolina Chapel Hill, Chapel Hill, NC
GRANT NO.: 5P01HD031921-08
KEYWORDS: adolescence (12-18), risk, health behavior, health survey, socioenvironment
TYPE STUDY: Cross-sectional Survey
AMOUNT: $50,000

The National Study of Adolescent Health: Survey 2000, is being conducted by investigators at the University of North Carolina, Chapel Hill, to investigate a broad set of research questions on the health of young men and women as they make the transition to adulthood. This survey is a follow-up to the National Longitudinal Study of Adolescent Health (Add Health). Add Health was conducted in 1994-96 to provide comprehensive information on adolescent health and behavior and the social contexts in which adolescents develop. Add Health was funded through a five-year grant supporting one wave of in-school data collection (1994; N=90,000), two waves of in-home data collection (N=20,000 and 16,000 respectively in 1995 and 1996), one wave of home interviews with parents of 18,000 respondents in 1995, two waves of data collected from school administrators, and linking of existing data on local communities. Survey 2000 is supported by a grant from the National Institute of Child Health and Human Development, with co-funding support from the DHHS Office of Population Affairs and Office of the Assistant Secretary for Health, and will re-survey 20,000 adolescents who initially participated in previous in-home interviews.

ALCOHOL AND OTHER SUBSTANCE ABUSE

TITLE: Alcohol, HIV Risk Behaviors, and Sexual Victimization — **NIAAA**
P.I.: Maria Testa, Ph.D.
INSTITUTION: Research Institute on Addictions, Buffalo, NY
GRANT NO.: 5R01AA12013-04
KEYWORDS: risk behaviors, HIV, sexual victimization, STDs, behavior
TYPE STUDY: Clinical
AMOUNT: $100,000

This application suggests that childhood sexual abuse and risk-prone personality (high sensation-seeking, high negative affect, low assertiveness) lead women to engage in risky behaviors (heavy alcohol and drug use, high levels of sexual activity and exposure to risky settings such as bars) which in turn increase the likelihood of experiencing both sexual victimization and HIV/STD infections. There will be a three wave cross-legged panel design using a representative sample of 1,000 unmarried women, ages 18-30, recruited from random digit dialing.

TITLE: Sexual Identity and Drinking: Risk and Protect Factors — **NIAAA**
P.I.: Tonda L. Hughes, Ph.D.
INSTITUTION: University of Illinois at Chicago, IL
GRANT NO.: 5K01AA00266-03
KEYWORDS: Alcohol, lesbians, substance abuse, behavior
TYPE STUDY: Clinical
AMOUNT: $55,224

This study will use an existing survey instrument to examine and compare risk and protective factors for heavy drinking and alcohol-related problems in lesbians and heterosexual women. The study will include data from 600 women who are 18 years of age or older.

TITLE: **Women with Schizophrenia & Co-Occurring Substance Use Disorders** **NIDA**
P.I.: **Jean Gearon, Ph.D.**
INSTITUTION: **University of Maryland, MD**
GRANT NO.: **5R29DA011199-03**
KEYWORDS: **schizophrenia, substance abuse, co-occurring substance use, HIV, risk factors, mental health**
TYPE STUDY: **Clinical**
AMOUNT: **$20,000**

The primary goals of this project are: 1) to determine if women with schizophrenia and co-occurring substance use disorders are more vulnerable to HIV (e.g., engage in more high risk behaviors) and violent victimization than either women with major depression and co-occurring substance use disorders or women with substance use disorders only and no history of serious and persistent mental illness; 2) to determine if women with schizophrenia who abuse substances experience more violent victimization than women with major depression and co-occurring substance use disorders, or women with substance abuse disorders alone and no history of serious and persistent mental illness, and 3) to examine the causal sequencing between cognitive functioning, social competency, negative symptoms and HIV risk and victimization.

CANCER

TITLE: **Growth Regulation of the Normal and Malignant Endometrium** **NCI**
P.I.: **Leslie Gold, Ph.D.**
INSTITUTION: **New York University School of Medicine, New York, NY**
GRANT NO.: **1R01CA89175-01A1**
KEYWORDS: **endometrial cancer, hormones in carcinogenesis, hormone therapy, cancer research**
TYPE STUDY: **Basic**
AMOUNT: **$100,000**

The broad long-term objectives of this study are to elucidate mechanisms that cause loss of growth inhibition by TGF-$ in endometrial adenocarcinoma (ECA) and to define hormone regulation of TGF-$ through stroma/epithelial interactions in the endocumetrium. ECA is induced by estrogenic (E2) agents causing hyperproliferation of uterine epithelial cells (UtE). Progesterone (Pg) is therapeutic due its growth inhibitory effect. TGF-$-mediated growth inhibition is transduced by two cooperating receptors (RI, RII) and the downstream signaling/transcription factors, Smad2/3, that activate genes that block cell cycle progression, such as the cyclin-dependent kinase inhibitor, $p27^{kip1}$. The investigators have shown that UtE isolated from all grades of ECA escape negative growth control by TGF-$ by incurring multiple defects in the TGF-$ response pathway including, loss of: TGF-$ RII, activated Smad2, and $p27^{kip1}$. Moreover, in complex hyperplasia (CH), the precursor to ECA, these proteins are already decreased. Thus, disruption of TGF-$ action occurs early in endometrial carcinogenesis, providing an opportunity to understand molecular events leading to dysregulated growth. The principle investigator will use primary cultures of normal, CH, and ECA UtE and co-cultures with stromal cells (UtS), which unlike ECA cell lines, retain many in vivo differentiation characteristics. Specific Aim I, will determine the molecular mechanisms causing TGF-$ receptor down regulation (e.g., transcriptional, translational) and test for defective Smad2/3 signaling using a TGF-$-promoter-responsive reporter assay. TGF-$ function by transient transfection of RII cDNA into ECA UtE will be regained. Specific Aim 2 will test the hypothesis that loss of $p27^{kip1}$ in ECA is by degradation via ubiquitin-proteasome pathway, which is E2-driven directly through as a MAPkinase via the Ras/MAPK/ERK1 pathway that TGF-$ normally prevents p27 degradation. Tissue/cell lysates, inhibitors of proteasomes and MAPK, and immuno-analytical techniques will be used. Using single cell and co-cultures, we show that UtS from normal but not malignant endometrium mediates Pg-induced growth inhibition of normal UtE. Specific Aim 3 will test the hypotheses that UtS paracrine-mediates Pg-induced growth inhibition of UtE by release of TGF-$ in response to Pg. Co-cultures of normal and "malignant" UtS and UtE and novel *in vivo* chimeric tissue recombinants composed of UtS from both, Pg receptor knock-out (PRKO) and wild-type mice and human UtE, that are hormonally manipulated as transplants in nude mice and UtE then analyzed for growth will be used. These studies should elucidate molecular mechanisms of endometrial carcinogenesis, hormonal (dys) regulation of endometrial growth, and identify targets for prevention and therapeutic intervention.

TITLE: **Clinical Trials of Two Human Papillomavirus (HPV)-like Particle Vaccines** **NCI**
P.I.: **Douglas R. Lowy, M.D.**
INSTITUTION: **NCI, Bethesda, MD**
KEYWORDS: **human papillomavirus, cancer, cervical, vaccine development, STDs**
TYPE STUDY: **Clinical**
AMOUNT: **$300,000**

This project will perform the early phase clinical trials of two HPV16-based papillomavirus vaccines. L1 is a major structural papilloma viral protein that can self-assemble into virus-like particles (VLPs). It is thought that L1 VLP will only protect by preventing primary infection. To add another level of protection, a chimeric VLP was developed by adding the L2 minor capsid protein to the L1. After preclinical vaccine results, an early phase human trial of L1 HPV16 VLP vaccine is being tested. There are four groups of 12 normal volunteers 18-29 years old. In each group, ten volunteers received the vaccine and two received a placebo in a double-blind fashion.

TITLE: **Symptom Intervention for Older Women with Breast Cancer** **NINR**
P.I.: **Susan M. Heidrich, Ph.D.**
INSTITUTION: **University of Wisconsin Madison, Madison, WI**
GRANT NO.: **1R01NR07741-01**
KEYWORDS: **quality of life, cancer research, breast cancer, behavior**
TYPE STUDY: **Clinical**
AMOUNT: **$100,000**

Older women, especially those over age 75, are the fastest growing segment of the population. Many of these women will be living with breast cancer because the incidence of this disease increases with age. Unfortunately, the research on adaptation to illness, symptom management, and quality of life of women with breast cancer has focused on women under 65. Unlike younger women, older women with breast cancer experience symptoms of their disease and its treatment concurrent with symptoms of age-related chronic illnesses. Thus, they are faced with the unique challenge of sorting out and managing a variety of complex and sometimes confusing symptoms. We propose to test an individualized representational intervention (IRIS) to improve symptom management and quality of life in older women with breast cancer. The theoretical basis of the intervention is Leventhal's Common Sense Model, with the addition of strategies for conceptual change. Leventhal's Common Sense Model suggests that individuals' representations of their symptoms are critical determinants of how they cope with them. By addressing women's representations, we hope to change beliefs that interfere with adequate symptom management, assist women in developing individualized, effective symptom management strategies and thereby improve quality of life. Participants in this study will be women aged 65 and older who are at least one year post-diagnosis of breast cancer. They will be randomized to one of three conditions: a representational intervention (IRIS) delivered by an advanced practice nurse in a counseling interview, an attention-only control group, or usual care. Measures of symptom distress, helpfulness of symptoms management activities, and quality of life will be taken at baseline, six weeks and ten weeks post intervention. We predict that IRIS will improve symptom management, which will in turn improve quality of life for older women with breast cancer.

CARDIOVASCULAR DISEASE

TITLE: **Evidence Report - Gender Differences in Cardiac Care** **AHRQ**
P.I.: **Deborah Grady, M.D.**
INSTITUTION: **Regents of the University of California, San Francisco, CA**
KEYWORDS: **cardiovascular disease, diagnostic testing, coronary artery classification score**
TYPE STUDY: **Collaborative Federal Agency Review**
AMOUNT: **$250,000**

The Phase II project builds upon the findings and recommendations from the initial study that identified the scientific evidence and basis relating to sex and gender differences in coronary heart disease, its diagnosis and subsequent treatment. The recommendations, considered by the Evidence Practice Centers and AHRQ, in order to complete a comprehensive evidence report on the prioritized set of questions that focus on the gender-based difference in diagnosis and treatment, both in-hospital and chronic, related to coronary heart disease. The study population is adult females, including major racial/ethnic minorities and the elderly.

TITLE: **Hormonal Regulation of Angiotensin Receptors** **NIA**
P.I.: **Kathryn Sandberg, Ph.D.**
INSTITUTION: **Georgetown University, Washington, DC**
GRANT NO.: **1R01AG19291-01**
KEYWORDS: **hypertension, cardiovascular disease, kidney, rennin-angiotensin system, estradiol, estrogen receptors, aging**
TYPE STUDY: **Basic**
AMOUNT: **$100,000**

The sexual dimorphism associated with many cardiovascular and renal disease related to aging is well documented with the risks being significantly higher for men than women. Two of the major risk factors in these diseases are felt to be increased activity of the renin angiotensin system (RAS) and estrogen deficiency. Furthermore, there is accumulating evidence that estrogen may have a regulatory influence on the RAS. In view of its considerable potential physiologic and pathophysiologic significance, the principle investigator will investigate how estrogen regulates the activity of the RAS. Specific hypotheses to be tested in the proposed studies are: 1) estrogen down-regulates the density of the type 1 angiotensin receptor subtype (AT_1) expressed in adrenal and kidney tissues and thereby attenates tissue responsiveness to the hormone, angiotensin II (Ang II); 2) estrogen mediates its effects on AT_1 receptor AT_1 receptor expression in these tissues via the estrogen type $ ($_{Er\$}$) receptor; 3) estrogen has direct effects on AT_1 receptor expression by modulating receptor transcriptional and/or posttranscriptional mechanisms; 4) estrogen also acts to decrease AT_1 receptor expression by modulating the local production of Ang II; and 5) the ability of estrogen to down-regulate Ang II activity in the adrenal and kidney is attenuated in animal models of salt-sensitive hypertension and aging. Our first aim is to determine the effects of estrogen on AT_1 receptor density in the adrenal and kidney of the rat using quantitative autoradiography under a variety of perturbations of the RAS. In Aim 2, the effects of estrogen on adrenal and kidney tissue responsiveness to Ang II by measuring the effects of estrogen on Ang II-induced changes in aldosterone secretion and renal hemodynamics will be determined. The third aim will focus on determining the specific mechanisms by which estrogen reduces the density of AT_1 receptors. The effect of estrogen on AT_1 receptor synthetic and degradative pathways, and its effects on the components of the plasma and tissue RAS will be determined. Which estrogen receptor subtype mediates the effects of estrogen will also be determined. In the last aim, the effects of estrogen on adrenal and kidney AT_1 receptor density and function in relevant animal models of salt-sensitive hypertension and aging will be studied. These studies will answer important questions about whether some of the well-documented cardio- and renal-protective effects of estrogen may occur via down-regulation of AT_1 receptors in the adrenal and kidney, two key effector organs of the RAS.

TITLE: **CVD Risk and Health in Postmenopausal Phytoestrogen Users** **NHLBI**
P.I.: **Donna C. Kritz-Silverstein**
INSTITUTION: **University of California San Diego, San Diego, CA**
GRANT NO.: **3R01HL057790-04**
KEYWORDS: **bone density, cardiovascular disease, dietary supplement, postmenopause, behavior, osteoporosis, prevention**
TYPE STUDY: **Clinical**
AMOUNT: **$144,795**

In the United States, heart disease is the leading cause of death in postmenopausal women. Estrogen replacement therapy is beneficial for heart disease risk factors as well as for bone density. However, a large proportion of postmenopausal women are not compliant with therapeutic regimens. Phytoestrogens are naturally occurring compounds found in plants and soy products that have estrogenic effects, and may represent an alternative treatment for the prevention of heart disease and osteoporosis in postmenopausal women. However, few intervention trials have examined the extent to which it is possible to improve heart disease risk factors, bone density, and quality of life in postmenopausal women through use of a dietary supplement of Phytoestrogen. The proposed randomized, double-blind, placebo controlled study is designed to determine the acceptability and benefits of use of a dietary supplement of Phytoestrogen (genistein) versus placebo on heart disease risk factors, bone density and psychosocial outcomes in postmenopausal women aged 45-74. Approximately 300 women will be screened in order to enroll 200 (100 treatment, 100 placebo) who will each be followed for one year. Data will be collected at screening and baseline visits, 1 and 3-month follow-up telephone calls, and 6- and 12-month follow-up clinic visits. Measures of HDL, and other heart disease risk factors, hip and spine bone density, and depression, life satisfaction, and quality of well-being will be obtained. Cross-sectional and longitudinal

comparisons of treatment and placebo groups will be performed before and after adjustment and stratification for potentially confounding covariates. It is expected that women treated with Phytoestrogen will have higher HDL and bone density, and more favorable psychosocial outcomes. It is also expected that women using Phytoestrogen will have more favorable total cholesterol, LDL, triglycerides, Lp(a), fibrinogen, blood pressure, fasting and postmenopausal challenge glucose and insulin, and fat distribution. Given that women can expect to live one-third of their lives after menopause, the investigators point out that it is important to know how Phytoestrogen may modify heart disease risk factors and bone density. They further state that by defining the influence Phytoestrogen use has, this study would contribute to understanding of how to prevent cardiovascular disease and osteoporosis in postmenopausal women and thereby improve their quality of life.

DIABETES

TITLE: **Diabetes Prevention Program (DPP)** **NIDDK**
Primary Prevention Program - Data Coordinating Center
P.I.: **Sarah Fowler**
INSTITUTION: **George Washington University**
GRANT NO.: **5U01DK048489-08**
KEYWORDS: **diabetes, non-insulin dependent diabetes mellitus, impaired glucose tolerance, prevention**
TYPE STUDY: **Clinical**
AMOUNT: **$67,500**

The Diabetes Prevention Program (DPP) is a multi-centered randomized trial designed to determine whether type 2 diabetes can be prevented or delayed in a population of high-risk individuals. Included in the high-risk population are women with a history of GDM and individuals with impaired glucose tolerance. There are 3.234 participants enrolled in the three-arm study with two active treatment groups (metformin and life-style) compared to placebo controls. Of the total recruited, 68% were women, 13% of these had a history of GDM, and nearly 50% were from minority populations.

TITLE: **Diabetes Prevention Program (DPP)** **NIDDK**
Primary Prevention Trial
P.I.: **David Marrero**
INSTITUTION: **Indiana Univ-Perdue University at Indianapolis, Indianapolis, IN**
GRANT NO.: **5U01DK048406-08**
KEYWORDS: **diabetes, behavior modification, prevention, gestational diabetes mellitus, weight control, clinical trials**
TYPE STUDY: **Clinical**
AMOUNT: **$67,500**

The primary goal of the proposed project is to determine, via a collaborative multicenter trial, whether interventions can: a) prevent persons with impaired glucose tolerance (IGT) or a history of gestational diabetes mellitus (GDM) from developing non-insulin-dependent diabetes mellitus (NIDDM); and b) prevent the worsening of glucose tolerance in people with newly diagnosed NIDDM. Because of the ethnic diversity of the study populations, a secondary goal is to design the interventions to be sensitive to varying social, ethnic, and cultural values. With the use of the Regenstrief Medical Record System, we have identified three potential high risk populations: a) 6721 persons with a prior history of diabetes with random blood glucose values of 108-160 mg/dl and concomitant risk factors for NIDDM, of whom 54% are African-American, b) 3688 patients with NIDDM in whom we will contact their first degree relatives, and c) between 530-600 women with a history of GDM projected to be available by enrollment, 34% of whom are African-American. We plan to evaluate, using a randomized control group comparison design, the relative effectiveness of the proposed interventions in reducing conversion to NIDDM in persons with IGT, and deterioration of glucose tolerance in newly diagnosed NIDDMs as primary end points and macrovascular risk glucose tolerance in newly diagnosed NIDDMs as primary end points and macrovascular risk factors, coronary events, and overall mortality as secondary end points.

TITLE: Diabetes Prevention Program (DPP) **NIDDK**
P.I.: Harry Shamoon
INSTITUTION: Yeshiva University, New York, NY
GRANT NO.: 5U01DK048349-08
KEYWORDS: diabetes, prevention, gestational diabetes mellitus, weight control, clinical trials
TYPE STUDY: Clinical
AMOUNT: $21,000

By selecting populations at higher than average risk for the ultimate development of NIDDM, the Diabetes Center at the Albert Einstein College of Medicine will test the following hypothesis: The reduction in risk of developing NIDDM in persons at high risk for the development of diabetes will be dependent on treatment which affects insulin resistance, islet B-cell dysfunction, and/or hepatic glucose production. Interventions which include diet, exercise sulfonylurea drugs, and metformin in a factorial design can address this hypothesis. The Albert Einstein Center has a large, identified population of individuals from racial and ethnic minority groups in the Bronx and Westchester Counties who receive their medical care in Einstein-affiliated programs; an identified and well characterized population of women who had gestational diabetes diagnosed between 1988 and the present, and an annual accrual of an additional cohort of women with gestational diabetes; members of the treatment team with specific competence in diabetes in Hispanic and in African-American individuals; expertise in related areas such as hypertension control, cardiovascular risk reduction, and behavioral techniques intended to achieve therapeutic goals.

TITLE: Diabetes Prevention Program (DPP) **NIDDK**
P.I.: Janet A. Tobian
INSTITUTION: University of Chicago, Chicago, IL
GRANT NO.: 5U01DK048381-08
KEYWORDS: diabetes, prevention, clinical trials
TYPE STUDY: Clinical
AMOUNT: $22,000

This grant is multi-center trial in which subjects would be screened for inclusion and exclusion criteria. A primary prevention subgroup will consist of subjects with impaired glucose tolerance (IGT) by National Diabetes Data Group (NDDG) criteria with a fasting plasma glucose (FPG) equal to or more than 110 mg/dl. A secondary intervention subgroup will consist of individuals with NIDDM by NDDG criteria and a FPG $\geq$ 140 mg/dl. The subjects will be randomized in a 2 x 2 factorial design to: 1) intensive program of diet, exercise and stress reduction versus standard dietary and exercise advice as well as 2) therapy with either glipizide or placebo. We propose that the diet/exercise intervention be modeled after the PATHWAYS program (diet, exercise and stress management) which has been validated as an effective method of weight reduction in inner city African-American women. Individuals will be followed to test whether these interventions can: 1) prevent the worsening of glucose tolerance in these subjects over 5 years and 2) reduce cardiovascular morbidity and mortality.

TITLE: NIDDM Primary Prevention Trial (DPT-2) **NIDDK**
P.I.: Neil White
INSTITUTION: Washington University, St. Louis, MO
GRANT NO.: 5U01DK048400-08
KEYWORDS: diabetes, gestational diabetes mellitus, prevention, clinical trial
TYPE STUDY: Clinical
AMOUNT: $22,000

The proposed intervention is centered on an intensive, multi-disciplinary, program to promote long-term weight loss and increase physical activity among 200 volunteers who work in or live near the Washington University Medical Center in St. Louis. The proposed intervention is designed to minimize physical discomfort and life style disruption, to emphasize gradual, moderate changes in the foods usually eaten, to maximize continued adherence over five years and to be acceptable to both white and African-American volunteers. In order to sustain this weight loss long term, it is proposed to have the intensively managed patients seen regularly by trained members of a multidisciplinary team that will consist of an exercise technician, a nutritionist, a nurse, and a social worker trained in behavioral medicine. Volunteers randomized to the control group will be seen quarterly and provided with state of the art educational and motivational materials that will include recommendations for weight loss, increase physical activity aid a prudent diet low in saturated fats and cholesterol.

EATING DISORDERS

TITLE: Meditation-Based Treatment for Binge Eating Disorder **NCCAM**
P.I.: Jean Kristeller, Ph.D.
INSTITUTION: Indiana State University, Terre Haute, IN
GRANT NO.: 1R21AT00416-01
KEYWORDS: healthy living, obesity, eating disorders, CAM, mental health, behavior
TYPE STUDY: Clinical
AMOUNT: $172,095

As many as 30% of individuals seeking treatment for obesity meet DSM-IV criteria for binge eating disorder (BED) (1). BED is marked by recurrent episodes fo binging, accompanied by feelings of loss of control, and involves chronic disregulation of physiological, emotional and behavioral systems (2). Meditation-based interventions have been used successfully to treat disorders with similar addictive and disregulatory characteristics (3). But have not been applied to treating BED. Data from an uncontrolled pilot study (4) suggests that such an intervention can have marked immediate impact on decreasing episodes of binge eating and other associated characteristics in obese women. Therefore, this study incorporates appropriate comparison conditions to further investigate the efficacy of a mindfulness meditation-based intervention as a treatment component for treating BED symptoms. Exploratory aspects include further development of a manual, establishment of effect size (in comparison to appropriate comparison groups), inclusion of a more diverse population, and of measures that address: 1) individual differences in treatment response, 2) possible mechanisms, 3) time course of response, and 4) impact on medical/health variables. Women (approximate N=162) from two communities will be randomly assigned to 3 conditions: 1) an 8-week manualized mediation-based group intervention, 2) a psychoeducational comparison condition, or 3) a waiting-list control. Primary outcome variables will be changes in binge eating behaviors, and associated measures of depression, anxiety, self-esteem, and diet; secondary variables include medical variables sensitive to dietary change (i.e., weight; blood pressure; lipid profile; blood glucose levels), and process variables related to meditation practice, such as the Tellegen Absorption Scale, perceived value and use of the meditation practice, and experiences of increased control and awareness. Participants will be evaluated pre- and post-treatment, and at 1, 3, and 6 months followup. This data would then support the further investigation of a meditation-based intervention as part of a more comprehensive treatment program for BED.

TITLE: Nociception in Bulimia Nervosa **NIDDK**
P.I.: Patricia Faris, Ph.D.
INSTITUTION: University of Minnesota, Minneapolis, MN
GRANT NO.: 2R01DK52291-06A2
KEYWORDS: bulimia nervosa, eating disorders, mental health
TYPE STUDY: Clinical
AMOUNT: $200,000

This application proposes to further study the role of vagal afferents in the perpetuation of binge-eating and vomiting. Previously proposed was that the pathophysiology of bulimia nervosa involved dysregulation of the afferent vagus nerve. This hypothesis was tested using two main strategies: (1) the use of somatic pain detection as a physiological marker of vagal afferent activity; and (2) the use of ondansetron (a 5 HT3 antagonist known to reduce vagal neurotransmission) as a pharmacological challenge test of vagal modulation of both the bulimic behaviors and on elevated pain detection thresholds. The principle findings from these studies are: (1) pain detection thresholds rise dynamically across the interval between bulimic binge/vomit episodes, apparently reaching their zenith as the next bulimic episode is approached and dropping to their nadir in close temporal association with having recently engaged in a bulimic episode; and (2) ondansetron treatment was associated with a significant moderation in both the cyclic fluctuations in pain detection thresholds and the primary disorder symptom of binge/vomit episodes per week in a group of patients with severe and chronic bulimia nervosa under randomized, placebo controlled, double-blind conditions. The overall hypothesis will be tested through an interactive combination of clinical pharmacology and psychophysiological approaches. Specific Aim I will investigate the association between disorder severity as indicated by binge/vomit frequencies and dynamic changes in pain detection thresholds. The approach of this Aim is based on the idea that if dynamic increases in vagal activity drive bulimic episodes, then the rate of cyclic changes in vagal activity should be a significant statistical predictor of the frequency of bulimic behaviors. Specific Aim II will investigate the effect of psychotherapeutic intervention on physiological indices of vagal activity, namely thresholds for pain detection and induction of satiety. The approach of the Aim is based on the idea that if vagal hyperactivity represents the critical factor involved in symptom production, then any therapeutic method resulting in a decrease in symptoms would be predicted to be accompanied by a demonstrable correction in vagal function. In addition to generating

important basic science information on vagus nerve function in bulimia nervosa, these studies will also provide insight into the utility of ondansetron in the clinical treatment of this debilitating disorder.

ENDOCRINOLOGY

TITLE: **Mechanisms of Steroid Hormone Action in Brain** **NIDDK**
P.I.: **Marc J. Tetel, Ph.D.**
INSTITUTION: **Skidmore College, Saratoga Springs, NY**
GRANT NO.: **1R55DK061935-01**
KEYWORDS: **estrogen, estrogen receptors, coactivators, brain, neurosciences research**
TYPE STUDY: **Basic**
AMOUNT: **$100,000**

The ovarian hormones, estradiol and progesterone, act in brain to mediate complex behaviors, such as female reproductive behavior in rodents. Understanding how these ovarian hormones act in brain is essential to understanding their role in various mental health disorders such as depression. However, the cellular and molecular mechanisms by which steroid receptors mediate the effects of these hormones in brain are not well understood. Recently, a novel class of proteins has been identified, known as nuclear receptor coactivators, that dramatically enhance the transcriptional activity of steroid receptors. While research has led to a much greater understanding of the molecular mechanisms of these coactivators in steroid receptor action in vitro, very little is known about coactivator function in vivo in brain to regulate hormone-dependent gene expression and behavior. This proposal investigates the function of three important coactivators, Steroid Receptor Coactivator-1 (SRC-1), SRC-3 and CREB Binding Protein (CBP), in estrogen receptor (ER) action in brain and the regulation of behavior. Aim I will determine if SRC-3, which has recently been shown to be essential for female reproductive physiology, is expressed in steroid receptor containing neurons in brain regions known to regulate reproductive behavior. In support, it has been found that SRC-1 and CBP are expressed in steroid sensitive cells in behaviorally-relevant brain areas. Aim I will also test the hypothesis that these three coactivators physically interact with neural ER in a hormone-dependent manner. Aim 2 will use antisense oligonucleotides to suppress SRC-1, SRC-3 and CBP expression to investigate the function of these coactivators in ER-mediated activation of three behaviorally-relevant genes: the progesterone receptor, preproenkephalin and oxytocin receptor genes. Aim 3 will use the same antisense approach to test the hypothesis that these nuclear receptor coactivators are critical for the expression of estradiol-induced female reproductive behavior. Consistent with these hypotheses, our preliminary results indicate a functional role for these coactivators in estrogen-dependent gene expression in brain and hormone-dependent reproductive behavior. These studies will greatly enhance our understanding of how these novel coactivators function with steroid receptors in brain to activate behaviorally-relevant genes and regulate complex behaviors. Finally, these nuclear receptor coactivators have been implicated in human disorders, including a form of mental retardation (Rubinstein-Taybi Syndrome) and hormone-dependent diseases such as breast cancer. Studying how these coactivators function in vivo, and moreover in brain, will greatly increase our limited knowledge of the role of these coactivators in human disorders.

GASTROENTEROLOGY

TITLE: **Cognitive Therapy as a Treatment for Irritable Bowel Syndrome (IBS)** **NIDDK**
P.I.: **Edward Blanchard, Ph.D.**
INSTITUTION: **State University of New York, Albany, NY**
GRANT NO.: **5R01DK54211-03**
KEYWORDS: **Irritable bowel syndrome, cognitive therapy, mental health, behavior**
TYPE STUDY: **Clinical**
AMOUNT: **$100,000**

Recent research suggests that cognitive therapy (CT) is highly effective (70-80% clinically improved) in the short-term (3 months) as a treatment for IBS. This application seeks to replicate and extend previous small-scale studies by conducting a controlled clinical trial of CT vs. a self-help support group as an attention placebo control and follow-up of the treated patients for at least 12 months.

TITLE: Neurotensin's Role in Models of IBS-Related Hyperalgesia **NIDDK**
P.I.: Robert E. Carraway, Ph.D.
INSTITUTION: University of Massachusetts, Worcester, MA
GRANT NO.: 3R01DK56999-01S1
KEYWORDS: Neurotensin, irritable bowel syndrome, stress responses, bowel hyperalgesia, neurosciences research
TYPE STUDY: Basic
AMOUNT: $50,000

Neurotensin (NT), a gastrointestinal peptide, participates in modulating pain perception, mediating stress responses and regulating digestive motility/secretion. NT works closely with mast cells which coordinate neuro-endocrine immune activities in the gut. This project hypothesizes that NT-mast cell interactions are involved in physiological visceral perception and/or pathological visceral hyperalgesia. It is likely that multiple chemical mediators are involved in visceral hypersensitivity associated with stress-related functional bowel disorders. This proposal will address the potential role of neurotensin as a key mediator of the pathological hyperalgesia associated with irritable bowel syndrome using animal models of post-stress and post-inflammatory bowel hypersensitivity. The hypothesis will be tested using NT receptor antagonist, an NT-knockout mouse model, and a mast cell deficient mouse model.

TITLE: Regional Cerebral Activation with Visceral Pain in IBS Controls **NIDDK**
P.I.: Howard R. Mertz, M.D.
INSTITUTION: Vanderbilt University, Nashville, TN
GRANT NO.: 3R21DK57047-01S1
KEYWORDS: Irritable bowel syndrome, limbic system, mental health, neurosciences research, behavior
TYPE STUDY: Clinical
AMOUNT: $25,000

Recent data have demonstrated abnormal activation of limbic and paralimbic pain centers in irritable bowel syndrome (IBS) in response to rectal pain. Conversely, non-limbic pain centers including the VPL-thalamus, sensory cortex and insular systems are critical to the generation of symptoms in IBS. This project will compare the activity of the limbic system in IBS and controls in response to graded rectal distention (non-painful and painful). Activity in non-limbic pain centers and autonomic outflow centers will be compared between IBS and controls. Understanding the function of the limbic and non-limbic pain centers in healthy and disease states, and the effect of stress and medication on the pain experience may lead to improved pharmacological and behavioral therapies for visceral pain, including IBS.

TITLE: Effect of Menstrual Cycle and IBS on CNS Processing of Gut Stimuli **NIDDK**
P.I.: Ann Ouyang, M.D.
INSTITUTION: Milton S. Hershey Medical Center, Hershey, PA
GRANT NO.: 3R21DK57053-02S1
KEYWORDS: Irritable bowel syndrome, menstrual cycle, anxiety, visceral sensitivity, mental health, neurosciences research
TYPE STUDY: Clinical
AMOUNT: $50,000

Recent evidence suggest that patients with irritable bowel syndrome (IBS) have heightened sensitivity to visceral stimuli. Little is known about factors affecting visceral sensitivity, reasons for the higher female prevalence, or the central nervous system processing of visceral sensitivity stimuli, and if this process is altered in IBS. The investigators hypothesize that: 1) menstrual cycle stage affects visceral sensitivity in both control female subjects and in subjects with IBS; 2) the areas of the brain which are activated by visceral stimulation are dependent on both the degree of distension and by the perception that the stimulus is painful; and 3) the areas of the brain activated in IBS subjects when the stimulus is painful differ from areas activated in control subjects, and that this difference may be due to the effect of anxiety. Specific aims of the study are: 1) to determine the effect of menstrual cycle on the perception of rectal balloon distention and transcutaneous nerve stimulation (TNS) in subjects without bowel symptoms (controls); 2) to determine the effect of menstrual cycle on these responses in subjects with IBS; 3) to compare the responses between controls and IBS subjects; 4) to determine the regions of the brain activated in response to rectal (non-painful and painful) and non-visceral (TNS) stimulation; and 5) to determine the influence of the state of anxiety on these parameters. An understanding of cerebral processing of non-painful and painful visceral stimuli will be helpful in defining the pathway for perceiving pain in the IBS and other functional gut disorders, and for directing therapy appropriately.

TITLE: **Biofeedback for Fecal Incontinence and Constipation** **NIDDK**
P.I.: **William E. Whitehead, Ph.D.**
INSTITUTION: **University of North Carolina, Chapel Hill, NC**
GRANT NO.: **3R01DK57048-01S2**
KEYWORDS: **Biofeedback, fecal incontinence, constipation, pelvic floor dyssynergia, behavior**
TYPE STUDY: **Clinical**
AMOUNT: **$75,000**

Among constipation patients, half are reported to have pelvic floor dyssynergia, a condition marked by an inability to relax pelvis floor muscles during evacuation. Biofeedback has been recommended for the treatment of both conditions because uncontrolled studies over the past 10-25 years suggest that these treatments are as effective as medical or surgical management and involve no risk. However, placebo-controlled trials are lacking in this area. The aims of the proposed research are: 1) to compare biofeedback to alternative therapies for which patients have a similar expectation of benefit; 2) to identify which patients are most likely to benefit; and 3) to assess the impact of treatment on quality of life. Two long-term, prospective, single-blind studies will be conducted. Study I will compare biofeedback for the treatment of fecal incontinence to a standard therapy, Kegel exercises. Study II will compare biofeedback for pelvic floor dyssynergia to a skeletal muscle relaxant drug (diazepam) and to placebo medication. These studies will help to establish the efficacy of biofeedback on the treatment of defecatory disorders.

GENITOURINARY

TITLE: **Urine Loss and Prolapse in Nuns and Their Parous Sisters** **NICHD**
P.I.: **Gunhilde M. Buchsbaum, M.D.**
INSTITUTION: **University of Rochester, Rochester, NY**
GRANT NO.: **1R01HD41165-01**
KEYWORDS: **reproductive health, gynecologic diseases, urinary incontinence, pelvic floor disorders, women's health**
TYPE STUDY: **Clinical**
AMOUNT: **$331,779**

Urinary incontinence (UI) and pelvic organ prolapse (POP) are common health problems in older women, for which the etiologies are poorly understood. Injuries to the pelvic floor at the time of vaginal delivery and genetic predisposition have been implicated as factors associated with UI and POP. However, the epidemiological evidence for these relationships is scant and controversial. Data from the investigators survey study of 149 nulliparous nuns found the same prevalence of stress urinary incontinence (SUI) as was reported for parous women. The major objective of our proposed study is to determine whether vaginal delivery and familiarity are associated with the development of urinary incontinence and pelvic organ prolapse by comparing the prevalence of objectively confirmed incontinenence and prolapse in nuns (nulliparous women) with the corresponding rates in their biological sisters who have had at least one vaginal delivery. To achieve this objective, the investigators will: recruit the nuns' biological sisters who have had at least one vaginal delivery; collect data from nuns and their sisters about the presence of any symptoms of UI and POP, and on any risk factors for these conditions; and examined nuns and sisters for objective evidence of UI and POP. The examiner will be blinded to the subjects' identity as to nun or sister, and to the presence or absence of symptoms. Women with signs or symptoms of UI and POP will undergo further urodynamic testing. Finally, the data collected will be tested in a matched pair analysis. It will be determined whether nulliparous nuns differ from their biological sisters with regard to UI and POP. A matched pair logistic regression will be performed to obtain an adjusted estimate of the impact of familiarity and vaginal delivery in UI and POP, taking into account other risk factors.

TITLE: **A Randomized Surgical Trial: Burch vs. Sling** **NIDDK**
P.I.: **Linda Brubaker, M.D.**
INSTITUTION: **Loyola University Chicago, Maywood, IL**
GRANT NO.: **1U01DK60379-01**
KEYWORDS: **urinary incontinence, minority women, women's health**
TYPE STUDY: **Clinical**
AMOUNT: **$115,000**

The Loyola team plans participation in the Urinary Incontinence Treatment Network in order to advance our understanding of the clinical care for women with stress urinary incontinence. Our multi-disciplinary team has the volume and proven ability to participate in clinical trials. As requested in the RFA, investigator experience, institutional support, patient volumes and human subject safety is discussed. The Loyola team understands the significance of this important clinical trial; can recruit and retain

patients of racial, economic and ethnic diversity; has experienced investigators, including physicians, nurses, physical therapists and urodynamic technicians; has a clinical environment and resources which will maximize chances for a successful clinical trial; has a current clinical practice which offers surgical, pharmacological and behavioral treatment for urinary incontinence; can ensure data management and transmission; and looks forward to cooperation with the other CTCs in order to maximize the scientific results of this study.

TITLE: **Maryland Interstitial Cystitis Clinical Trials Group** **NIDDK**
P.I.: **Susan Keay, M.D. & John Warren, M.D.**
INSTITUTION: **University of Maryland School of Medicine, Baltimore, MD**
GRANT NO.: **5U01DK054125-04**
KEYWORDS: **inflammation, interstitial cystitis, women's health**
TYPE STUDY: **Clinical**
AMOUNT: **$100,000**

Interstitial cystitis (IC) is a chronic disease characterized by pain, urgency, and frequency and by bladder findings of ulcers, glomerulations, and diminished capacity. The etiology(ies) is unknown and numerous treatments have been examined by only a few in well-designed trials. Patients would benefit from scrutiny of existing and novel treatments, the mission of the IC Clinical Trials Group (IC CTG). Critical to the IC CTG is the ability to recruit IC patients for well designed clinical trials. Over the last 7 years, work with IC patients has been to explore the pathogenesis of IC. The investigators have discovered a urine peptide which inhibits the growth of human bladder epithelial cells *in vitro* in 85% of IC patients vs. <10% controls. To explore the clinical role of this peptide, a recently modest recruitment campaign has begun and the investigators have observed a pent-up demand of IC patients and of urologists/gynecologists for IC research. Within a two month period, 241 patients have expressed willingness to participate in the clinical studies and 151 urologists/gynecologists have offered to refer the investigators >500 IC patients for these studies. The Baltimore-Washington area comprises more than 6,000,000 people. This includes many IC patients and the investigators will work with the ICA and the network of urologists/gynecologists to recruit large numbers of patients during the clinical trials. To respond to this clinical opportunity, a multidisciplinary team has been developed comprised of veteran IC investigators, urologists, and urogynecologists, skilled in bladder diseases and pain syndromes. This team has experience in complex projects, randomized placebo-controlled double-masked trials, large data sets, and collaborative ventures. This group will bring to the IC CTG experienced, motivated, and dedicated investigators; a new cadre of IC patients; and a network of referring urologists/gynecologists to study management strategies for this distressing disease.

HIV/AIDS

TITLE: **A Clinical Trial of DOT for HAART in Jailed Drug Users** **NIDA**
P.I.: **Jacqueline P. Tulsky, M.D.**
INSTITUTION: **University of California San Francisco, San Francisco, CA**
GRANT NO.: **1R01DA13892-01A1**
KEYWORDS: **criminal justice system, STDs, substance abuse**
TYPE STUDY: **Clinical**
AMOUNT: **$146,323**

HIV-infected adults in the United States corrections system are predominantly active drug users and people of color. These are the very populations with HIV who are not benefitting from effective treatments for HIV, such as highly active antiretroviral therapy (HAART). Jail may be an excellent site for the introduction of medical care for HIV to marginalized populations, particularly drug users who access care for HIV infection at lower rates than other populations of HIV-infected persons. Both primary medical care and initiation or continuation of treatment with HAART may be offered in jail. The jail setting also provides an ideal opportunity to evaluate the best way to deliver care in order to maximize the benefits both while in jail and, perhaps more importantly, after release from jail. Directly observed therapy (DOT), in which every dose of medication is observed, has been shown to decrease HIV viral replication in incarcerated inmates. Other benefits of DOT include sustained HIV viral control that minimizes the likelihood of developing drug resistance to HAART medications started in jail. In the San Francisco City and County jails, DOT is standard care for inmates on HAART. Unfortunately, our pilot data suggest that the benefits of DOT are often not sustained after inmates are released from jail and must transition to self-administered therapy. Alternatively, a structured program of self-administered therapy in jail may be an equally effective strategy as DOT while inmates are in jail and, may enable inmates to maintain virologic control after they are released from jail.

The effects of an intervention for delivering HAART to HIV-infected persons in jail (structured self-administered therapy), as compared to usual care (DOT), on virologic and immunologic outcomes in jail and after release from jail is proposed. The specific aims of this randomized, controlled trial of HAART in jailed drug users are: A.1 - Primary Aim 1: To compare the effects of structured self-administered therapy as compared to DOT on virologic and immunologic outcomes and incidence of developing new resistant mutations after release from jail; A.2 - Primary Aim 2: To compare the effects of structured self-administered therapy as compared to DOT on virologic and immunologic outcomes while subjects are in jail; and A.3 - Secondary Aim: To measure other factors that may be associated with the short-term and long-term virologic and immunologic outcomes. Such covariates include: demographic factors (including housing and employment); drug and alcohol use; general health status (physical and mental health status); and medications (lifetime and current HAART and medication adherence).

TITLE: **A Contextual Model of Microbicide Acceptability** **NIMH**
P.I.: **Kathleen M. Morrow, Ph.D.**
INSTITUTION: **Miriam Hospital/Brown Medical School, Providence, RI**
GRANT NO.: **1R01MH64455-01**
KEYWORDS: **microbicide, mental health, behavior, prevention**
TYPE STUDY: **Clinical**
AMOUNT: **$100,000**

Women are the fastest growing segment of the HIV/AIDS population, and heterosexual vaginal intercourse is their greatest risk factor. This growth, the lack of clear efficacy of more traditional prevention strategies, and ongoing questions about the safety and efficacy of Nonoxynol-9 in the prevention of HIV transmission, demands increased attention to the development of safe, effective vaginal microbicides. As these products are developed and investigated, it is also essential to establish an understanding of how acceptability and use of the products are decided by consumers. The common, one-factor approach of equating acceptability and use fails to capture the complex, contextual nature of microbicide acceptability and use. The present study applies a theoretical framework for understanding acceptability and, ultimately, its use among women at risk. Guided by the social ecology model, the investigator considers both product and person-in-context variables. The objective of this work is to elucidate how personal, social, relational, and political variables to one another and to a woman's decision to use a microbicidal product. Further, this study will address a limitation in the current state of microbicide acceptability research. That is, the present research will both contribute to a social ecological model of microbicide acceptability and develop a psychometrically sound, quantitative microbicide acceptability instrument. This tool will enable future research to quantify relationships and pathways between person-in-context factors, product characteristics, intention to use, and actual use of microbicides. The instrument will enable the investigators to compare factor structures across risk groups and will also provide the field with a high quality acceptability measure that will facilitate comparison and consolidation of data across studies. By contributing both to a theoretical and applied understanding of acceptability, and furnishing a sound means of quantifying product acceptability, this work will ultimately increase efficiency of acceptability assessment in upcoming Phase II/III clinical trials of vaginal microbicides, and allow for more successful education and marketing of approved microbicidal products.

IMMUNITY/AUTOIMMUNITY

TITLE: **Curcumin Treatment of Fibrosis** **NCCAM**
P.I.: **Stanley Hoffman, Ph.D.**
INSTITUTION: **Medical University of South Carolina, Charleston, SC**
GRANT NO.: **1R21AT00382-01A1**
KEYWORDS: **autoimmunity, scleroderma, CAM**
TYPE STUDY: **Basic**
AMOUNT: **$178,750**

Practitioners of alternative medicine recommend curcumin, a component of the spice turmeric, as a treatment for autoimmune diseases. Scleroderma is a debilitating autoimmune disease that affects over 100,000 people in the U.S., mostly women. The hallmark of scleroderma is dermal fibrosis. When accompanied by visceral organ fibrosis, significant morbidity and mortality results. Despite its widespread occurrence, little is known to suggest effective treatment. As part of a long-term objective of understanding the aberrant regulation of extracellular matrix protein accumulation in scleroderma, the investigators treated primary fibroblast cultures from the lungs of scleroderma patients with curcumin. They found that this treatment inhibits collagen accumulation and promotes cell death in these cultures while having no effect on normal lung fibroblasts. Interestingly, these effects of curcumin on scleroderma fibroblasts are enhanced in the presence of vitamin C. If curcumin were to have the same effect on scleroderma fibroblasts in vivo as it has in culture, then curcumin would be likely to be an effective treatment for

scleroderma. While curcumin is not yet used in standard medical practice, in Chinese and Indian folk medicine turmeric is used to treat a broad range of ailments. Published articles show curcumin to have a range of potent biological activities including anti-cancer, anti-inflammatory, and antimicrobial. The use of curcumin in folk medicine, published studies on curcumin, and the investigation studies combine to indicate that curcumin is non-toxic and is a treatment already used in alternative medicine that is likely to have demonstrably positive effects on patients with scleroderma and other fibrotic diseases. In order to test the hypothesis that curcumin may be a beneficial treatment for scleroderma in particular and fibrotic diseases in general, this study will: 1) Use cultured fibroblasts to determine the molecular and cellular mechanisms involved in the specific effects of curcumin on cells from scleroderma patients and 2) Perform translational research using an animal model for scleroderma and lung fibrosis to determine whether curcumin is indeed effective in treating lung fibrosis in vivo. These experiments will demonstrate the efficacy and the scientific basis for that efficacy of a disease treatment already recommended by practitioners of alternative medicine.

TITLE: **Visual Dysfunction and Quality of Life in Multiple Sclerosis** **NEI**
P.I.: **Laura J. Balcer, M.D.**
INSTITUTION: **University of Pennsylvania, Philadelphia, PA**
GRANT NO.: **1R01EY13273-01A1**
KEYWORDS: **visual impairment, Quality of Life, Multiple Sclerosis, autoimmunity, behavior**
TYPE STUDY: **Cohort Study**
AMOUNT: **$125,000**

Visual impairment is a leading cause of symptoms in patients with multiple sclerosis (MS). The extent to which vision has been affected by new therapies for MS is not known, and has been difficult to assess using traditional measures of neurologic impairment. The visual profile of MS has not been examined, and the relation of visual function to overall neurologic impairment in patients with MS has not been determined in a large, heterogeneous cohort. This proposal will accomplish the following specific aims: 1. Define the visual profile of MS in a large cohort (400 patients), and determine which measures best identify visual dysfunction in patients with MS; and 2. Determine the relation of visual function to vision- and disease-specific HRQOL in patients with MS.

TITLE: **Autoimmunity Center of Excellence** **NIAID**
P.I.: **Leonard Chess, M.D.**
INSTITUTION: **Columbia University College of Physicians & Surgeons, New York, NY**
GRANT NO.: **5U19AI46132-02**
KEYWORDS: **Multiple Sclerosis, Type 1 diabetes, scleroderma, systemic lupus erythematosus, rheumatoid arthritis**
TYPE STUDY: **Clinical**
AMOUNT: **$75,000**

This Center will establish an interdisciplinary basic and clinical research program to focus on the evaluation of novel therapeutic approaches to five autoimmune diseases: rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes, and scleroderma. The investigators hypothesize that there are four principal events involved in the immunopathogenesis of these diseases: 1) predisposing genes establish a T-cell repertoire capable of recognizing self peptides intrinsic to the autoimmune process; 2) previously tolerant autoreactive CD4+ T-cell clones become activated and expand to change the T-cell repertoire to reflect autoreactive effector T-cells; 3) regulatory mechanisms, including the activation of TH1 and TH2 CD4+ T-cell subsets as well as those involving CD8 T-Cells fail, through processes such as clonal deletion or changes in the cytokine milieu; and 4) pathogenic autoantibodies develop through cognitive T-cell B-cell interactions which effect tissue injury. In these diseases one would predict that reducing the clonal expansion of relevant autoreactive T-cell by blockade of T-cell receptor signaling or interruption of the CD40 ligand-dependent pathway could down modulate disease activity. Also, interruption of the inflammatory effector functions of T-cell mediated by TNF or CD40L would similarly reduce disease potential. These hypotheses will be tested during the natural history of disease and during specific immune interventions.

TITLE: Virginia Mason/UCHSC Autoimmune Center **NIAID**
P.I.: George S. Eisenbarth, M.D.
INSTITUTION: University of Colorado, Denver, CO
GRANT NO.: 1U19AI50864-01
KEYWORDS: autoimmunity, diabetes, Rheumatoid Arthritis
TYPE STUDY: Translational
AMOUNT: $200,000

This grant consists of 3 research projects. The overall objective of this application is to derive markers of autoimmune disease in its preclinical phases that would allow identification of individuals at high risk and the design of a rational prevention strategy. The projects deal in genetic, immunologic and environmental determinants that lead to disease. Project 1 will use tetramers to analyze the peripheral antigen-specific T cell profile in IDDM. Project 2 will identify three cohorts of individuals at increased risk for RA and attempt to define immunologic markers for this risk and subsequently derive prevention strategies based on this information. The third project will identify three population-based cohorts at high risk for celiac disease and study these for environmental and genetic factors leading to disease.

TITLE: Autoimmunity: Treatment by Co-stimulatory Signal Blockade **NIAID**
P.I.: Samia J. Khoury, M.D.
INSTITUTION: Brigham and Women's Hospital, Boston, MA
GRANT NO.: 5U19AI46130-02
KEYWORDS: Multiple sclerosis, inflammatory bowel disease, psoriasis, autoimmunity
TYPE STUDY: Clinical
AMOUNT: $75,000

A Center of Excellence for Autoimmunity will be established at the Brigham and Women's Hospital. Projects supported under this initiative will focus on the study of therapy of autoimmune diseases by blocking co-stimulatory signals. Investigators will focus on the CD40-CD40L pathway. The human diseases of major focus are multiple sclerosis, inflammatory bowel disease, and psoriasis. All are organ specific diseases where T-cells appear to be essential in initiating the immune response and lead to the particular disease pathology. Four projects are supported. The overall goals of project 1 are to study in a pilot trial the efficacy and safety of anti-CD40L therapy in multiple sclerosis. The goals of project 2 are to study in a pilot trial the efficacy and safety of anti-CD40L therapy in inflammatory bowel disease. Project 3 will focus on the immunologic changes associated with anti-CD40L therapy in patients with multiple sclerosis and inflammatory bowel disease. Project 4 will study the immune mechanisms of psoriasis. Data obtained from the pilot studies will be useful in designing Phase m clinical trials, and immunologic investigations will help to identify surrogate markers for disease activity.

TITLE: Denver Autoimmunity Center of Excellence **NIAID**
P.I.: Brian L. Kotzin, M.D.
INSTITUTION: University of Colorado Health Sciences Center, Denver, CO
GRANT NO.: 5U19AI46374-03
KEYWORDS: Type 1 diabetes, lupus nephritis, Rheumatoid Arthritis, kidney
TYPE STUDY: Clinical and basic
AMOUNT: $75,000

A Center of Excellence for Autoimmunity will be established at the University of Colorado Health Sciences Center. The Center builds on a strong research and clinical base in Type 1 diabetes, celiac disease, systemic lupus, rheumatoid arthritis, multiple sclerosis, autoimmune skin disease, autoimmune pulmonary disease and other autoimmune disorders. Under this initiative, two clinical trials will be conducted. Clinical Project 1 will evaluate subcutaneous insulin vaccination to prevent the appearance anti-islet autoantibodies in infants at high risk for the development of autoantibodies and disease. Clinical Project 2 will test humanized anti-C5 mAbs in patients with active lupus nephritis. Three basic components will be studied: 1) to define the T-cell specificities and distribution of insulin-and islet antigen-reactive T-cells in murine models and patients with Type 1 diabetes; 2) to determine the effects of inhibition of IL-18 and complement on cytokine production and disease in collagen-induced arthritis and rheumatoid synovion; and 3) to define the non-MHC genetic contributions to different clinical subtypes of autoimmune polyendocrine syndrome II. These basic projects will provide important information to design future clinical trials, to monitor the effectiveness of immunologic therapies, and/or provide surrogate markers to correlate with immunologic therapies in autoimmune diseases.

TITLE: **Mechanism of Copaxone Therapy in Multiple Sclerosis** **NIAID**
P.I.: **Michael Racke, M.D.**
INSTITUTION: **UT Southwestern Medical Center at Dallas, TX**
GRANT NO.: **5R01A147133-03**
KEYWORDS: **Multiple sclerosis, autoimmunity**
TYPE STUDY: **Clinical**
AMOUNT: **$140,000**

Multiple Sclerosis (MS) patients are categorized on the basis of whether they have clearly defined relapses, relapsing-remitting MS (RRMS), or whether they are progressing. Progressing patients are further divided on the basis of whether they initially experienced relapses (secondary progressive MS), or whether they deteriorate slowly without evidence of relapses or remissions (primary progressive MS). One question is whether the patients with primary progressive MS (PPMS) differ from the patients with secondary progressive MS or whether they represent different aspects of a clinical pathologic spectrum. This group has shown that patients with RRMS have myelin-reactive T cells that are less dependent upon costimulation than myelin-reactive T cells from normal controls. The goal is to test the hypothesis that myelin-reactive T cells in patients with PPMS can be distinguished from naive myelin-reactive T cells by a lack of dependence upon costimulation for activation and that costimulatory requirements for these myelin-reactive T cells change during the course of disease. Glatiramer acetate (Cop-1, Copaxone) has previously been shown to reduce the number of relapses in RRMS and is now being tested for efficacy in patients with PPMS. It is unclear how Copaxone exerts its therapeutic effect. This study will determine whether Glatiramer alters cytokine secretions of myelin-reactive T cells and the T cell repertoire in PPMS.

TITLE: **Penn Autoimmunity Center of Excellence** **NIAID**
P.I.: **A.M. Rostami, M.D., Ph.D.**
INSTITUTION: **University of Pennsylvania, Pennsylvania, PA**
GRANT NO.: **5U19AI146358-02**
KEYWORDS: **Multiple Sclerosis, systemic lupus erythematosus, autoimmunity**
TYPE STUDY: **Clinical and basic**
AMOUNT: **$75,000**

A Center of Excellence for Autoimmunity at the University of Pennsylvania School of Medicine will be established. It will consist of four projects (three clinical and one basic) and two cores. The clinical component of the Center consists of three clinical trials: 1) a Phase I/II trial on the use of antibody to Interleukin-12 for the treatment of multiple sclerosis; 2) a Phase I/II trial on the use of Interleukin-12 in the treatment of inflammatory bowel disease; and 3) the use of anti-CD20 antibody for the treatment of systemic lupus erythematosus. The basic science component is focused on the elucidation of the basic mechanisms of autoimmunity and immuno-modulation related to the clinical trials. Investigators will study the role of IL-12 in the pathogenesis and therapy of multiple sclerosis and its animal counterpart, experimental autoimmune encephalomyelitis. Also, they will focus on the mechanisms of anti-B-cell therapy in systemic lupus erythematosus and its murine model. An immunology core and an administrative core will be supported under this initiative.

TITLE: **T-Cell Reconstitution After Stem Cell Autograft** **NIAID**
P.I.: **Jan Storek, MD, Ph.D.**
INSTITUTION: **Fred Hutchinson Cancer Research Center, Seattle, WA**
GRANT NO.: **5R01A146108-02**
KEYWORDS: **autoimmunity**
TYPE STUDY: **Clinical**
AMOUNT: **$60,000**

The goal is to evaluate how the T cell repertoire is reestablished in patients with autoimmune diseases who have undergone lymphocytopenia from high dose chemotherapy/radiation plus anti-thymocyte globulin followed by reconstitution with autologous transplantation of hemopoietic (CD34+) precursors. The hypothesis is that in young individuals, a substantial number of regenerating T cells originate from hemopoietic progenitors whereas in older individuals, the vast majority of T cells originate from the expansion of preexisting T cells. The techniques used will be spectra typing, sequencing of the T cell receptor genes withing a single spectra typing band and quantifying T cells that contain T cell receptor-rearrangement circles.

TITLE: How Does Blockage of CD40/CD40L Prevent Autoimmunity? **NIAID**
P.I.: Matthias Von Herrath, M.D.
INSTITUTION: Scripps Research Institute, La Jolla, CA
GRANT NO.: 1U19AI50924-01
KEYWORDS: autoimmunity, diabetes
TYPE STUDY: Basic - Animal Models
AMOUNT: $100,000

This grant consists of two Pilot Projects, three Projects, and two Cores. Investigators will use three different models of autoimmune diseases to analyze effector functions of dendritic cells, lymphocytes, and regulatory antigen presenting cells. The Program focuses on the blockade of a single pathway and it's study in several different autoimmune scenarios. The program utilizes some novel techniques and is studying the detailed mechanism by which CD40L blockade effectively prevents the development of autoimmunity.

TITLE: Gene Mapping in Women with Systemic Lupus Erythematosus **NIAMS**
P.I.: Timothy W. Behrens, M.D.
INSTITUTION: University of Minnesota, Minneapolis, MN
GRANT NO.: 2R01AR43274-06
KEYWORDS: systemic lupus erythematosus, genetics of complex diseases, HLA mapping, autoimmunity
TYPE STUDY: Clinical
AMOUNT: $245,818

This study plans to map and eventually identify the susceptibility genes for human systemic lupus erythematosus. Over 250 SLE sib-pair and multiplex families, as well as 130 trio (affected SLE patient with both parents) families have been recruited. Genome-wide marker screens have been performed in these Minnesota pedigrees, and several chromosomal regions that appear likely to harbor SLE susceptibility genes have been identified. Dense microsatellite marker mapping has been initiated in several chromosomal regions that show the most convincing evidence for linkage in our family collection (1q41, 6p21 (HLA), 16q21, 20q, and 20p). More recently, analyzing several candidates genes in these regions have begun. This collection of SLE families is one of the largest in the world, and the investigators are well poised to move this project forward in the next funding period. In the next five years, the investigators propose to continue collecting additional SLE sib-pair and trio families, with a goal of recruiting 125 sib-pair families and 300 trios. In addition, a group of 200 age-, sex- and ethnicity-matched control individuals for case/control association studies with the accumulated marker data will be collected. The location of the susceptibility loci within the HLA region using the recombinant ancestral haplotype approach, and then attempt to identify the sequence variations within the HLA that confer risk for SLE will be further refined. Fine mapping in the non-HLA chromosomal regions that show linkage to the lupus phenotype will be continued. Within the time frame of the next five years the investigators hope to begin identifying the disease-associated sequence polymorphisms that confer risk for human SLE. The identification of the lupus genes will be critically important for furthering our understanding of this disease, and for rationally targeting new therapies.

TITLE: Studies of Collagen Gene Regulation in Two Murine Models **NIAMS**
P.I.: Stephen H. Clark, Ph.D.
INSTITUTION: University of Connecticut, Farmington, CT
GRANT NO.: 1R01AR48082-01
KEYWORDS: Scleroderma, fibroblasts, microarrays, autoimmunity
TYPE STUDY: Basic - Animal Models
AMOUNT: $200,000

This research project will utilize two mouse mutations that are models for Scleroderma, tight skin (Tsk) and tight skin2(Tsk2). Both mutations display excessive accumulation of collagen and other extracellular matrix components in the skin, a hallmark of the human disease. The long-range objective of this research is to utilize the two mutations, combined with several lines of transgenic mice as experimental tools, to dissect molecular mechanisms of disease pathogenesis.

TITLE: **Immune Mechanisms of Anti-CD40L Trial in Systemic Lupus Erythematosus** **NIAMS**
P.I.: **Syamal Datta, MD**
INSTITUTION: **Northwestern University, Evanston, IL**
GRANT NO.: **5R01AR046309-02**
KEYWORDS: **Lupus, autoimmunity**
TYPE STUDY: **Clinical**
AMOUNT: **$50,000**

CD40L is hyper-expressed by lupus B cells for abnormally prolonged periods, thus sustaining the production of pathogenic autoantibodies. A brief therapy of three injections of anti-CD40L in one week into lupus mice prevents the development of nephritis for more than a year. This clinical trial provides an opportunity to study the effects of anti-CD40L on the human immune system in vivo, particularly on the cells participating in the chronic ongoing autoimmune response in lupus patients. This study will examine the status of autoimmune T and B cells that are involved in the production of pathogenic anti-nuclear autoantibodies, before, during, and after therapy .

TITLE: **'c-Jun N -terminal kinase and joint destruction in RA'** **NIAMS**
P.I.: **Gary S. Firestein, M.D.**
INSTITUTION: **University of California, San Diego, School of Medicine, La Jolla, CA**
GRANT NO.: **1R01AR47825-01**
KEYWORDS: **Rheumatoid Arthritis, autoimmune disease, cytokine signaling**
TYPE STUDY: **Clinical**
AMOUNT: **$100,000**

Rheumatoid arthritis (RA) is a chronic inflammatory arthritis marked by synovial hyperplasia with local invasion of bone and cartilage. Accumulating evidence suggests that RA fibroblast-like synoviocytes (FLS), which form the leading destructive front of rheumatoid synovium, possess unique characteristics and contribute to cartilage degradation. Recently, it has been demonstrated that RA FLS activate the Jun N-terminal kinase (JNK) pathway efficiently and that this kinase is phosphorylated in RA synovium. To explore the potential relationship between JNK activation and joint damage in RA, the investigators will evaluate the signal transduction and transcription factor pathways involved in matrix metalloproteinase gene regulation, cartilage invasion, and joint destruction. In particular, the investigators will determine the contribution of the mitogen-activated protein kinase (MAPK) family. Preliminary experiments suggest that JNK is a key regulatory element in the machinery involved in joint destruction. In addition, IL-1-induced JNK phosphorylation is increased in RA and this pathway appears to regulate collagenase gene expression. The hypothesis that JNK is a target for development of chondroprotective agents in arthritis using two unique tools is proposed: 1) SP600125, the first small molecule selective JNK inhibitor; and 2) JNK knockout mice. First, the role of JNK in synoviocyte metalloproteinase production, cytokine expression, and invasion into cartilage will be determined. Second, the upstream signal transduction pathyways that regulate JNK in RA FLS will be determined. Finally, the role of JNK in animal models of arthritis will be determined. These data will support the hypothesis that JNK plays a role in the FLS biology and is a potential target for chondroprotective therapy.

TITLE: **Cellular and Genetic Basis of Systemic Lupus Erythematosus** **NIAMS**
P.I.: **Shu-Man M. Fu, M.D.**
INSTITUTION: **University of Virginia, Charlottesville, VA**
GRANT NO.: **1R01AR47988-01**
KEYWORDS: **systemic lupus erythematosus, autoimmune disease, genetics of complex disorders, kidneys**
TYPE STUDY: **Basic**
AMOUNT: **$185,000**

Systemic lupus erythematosus (SLE) is an autoimmune disorder affecting multiple organs with considerable morbidity and mortality. The disorder is characterized by multiple autoantibody production including antinuclear antibodies (ANA) and anti-ds DNA antibodies with immune complex formation leading to intense inflammation and end organ damage. Immune complex-mediated glomerulonephritis (GN) is a major manifestation of this disorder. Both genetic and environmental factors play important roles in its pathogenesis. Our laboratory has focused on the origin(s) of the autoantibodies detected in SLE and the genetic factors important in the generation of ANA and anti-dsDNA antibodies and lupus nephritis. Recently, a new model of SLE NZM2328 has been characterized. In this strain, there is female bias for ANA and chronic GN. In a backcross (NZM2328 X C57L/J F1) X NZM2328 analysis, a genetic interval has been identified on chromosome 1 in NZM2328 to control the development of chronic GN. An interval on chromosome 4 was shown to be linked to the production of ANA and anti-dsDNA antibodies. By a marker assisted

method, two congenics NZM2328.C57Lc1 and NZM2328.C57L.c4 were generated by moving the genetic segments of interest from chromosomes 1 and 4 respectively from C57L/J to NZM2328. In NZM2328.C57Lc1 little ANA, anti-dsDNA or chronic GN were seen. In contrast the NZM2328.C57Lc4, chronic GN was detected despite marked reductions in ANA and anti-dsDNA, dissociating ANA and anti-dsDNA production from lupus nephritis. It appeared that the genetic segment on chromosome 1 controls lupus nephritis and regulates ANA and anti-dsDNA production. These genetic loci have been named Lnc1, the lupus nephritis controlling gene 1 and Adn1, the anti-dsDNA and ANA production gene 1. For this proposal, Lnc1 is assumed to be different from Adn1. This application is focused on the elucidation of the cellular and immunochemical basis for autoantibody production and the generation of GN and to identify the genes, Lnc1 and Adn1. Four species aims proposed are (1) to characterize further NZM2328 and its two congenic lines NZM2328.C57Lc1 and NZM2328.C57Lc4; (2) to determine the specificities of immunoglobulins eluted from diseased kidneys from NZM2328.Lc4, clarifying the basis for the dissociation of anti-dsDNA antibody and ANA production from severe proteinuria and chronic GN; (3) to determine the cellular basis of severe proteinuria, chronic GN, and autoantibody production by adoptive cell transfer analysis; and (4) to generate intra c1 congenic recombinant stains from the parental strain NZM2328.C57Lc1, which contain smaller genetic intervals of chromosome 1 derived from C57L/J to determine the minimal C57L/J genetic segment(s) to suppress anti-dsDNA antibody and ANA production, and/or severe proteinuria and chronic GN. Thus, this study will refine the genetics for this interval so that the genes, Lnc1 and Adn1 may be identified, relevant to the phenotypic expression by positional cloning. The results from these experiments will provide further understanding of the pathogenesis of SLE. This information should lead to orthologous gene(s) identification in the SLE patients and provide potential targets for more specific and novel therapeutic interventions.

TITLE: **Fine Specificity of Scleroderma Autoantibodies** **NIAMS**
P.I.: **Judith James, M.D.**
INSTITUTION: **Oklahoma Medical Research Foundation, Oklahoma, OK**
GRANT NO.: **1R01AR48045-01**
KEYWORDS: **Scleroderma, immune response, clinical research, autoimmunity**
TYPE STUDY: **Translational**
AMOUNT: **$200,000**

This application addresses the important problem of the significance of autoantibodies in Scleroderma patients. The project proposes to identify the initial epitope on nRNP and topoisomerase I which is identified by sera from patients with Scleroderma. This will lead to the search for a pathogen in the environment which could lead to an immune response to the cross-reacting antigen. The possibility of tissue damage due to autoantibodies will also be investigated.

TITLE: **Registry and Repository of African Americans with Rheumatoid Arthritis** **NIAMS**
P.I.: **Larry Moreland, M.D.**
INSTITUTION: **University of Alabama at Birmingham, Birmingham, AL**
GRANT NO.: **1N01AR002247-000**
KEYWORDS: **African American, Rheumatoid Arthritis, autoimmunity**
TYPE STUDY: **Clinical**
AMOUNT: **$200,000**

This 5-year project will be housed at the University of Alabama at Birmingham. It will establish a Consortium for the Longitudinal Evaluation of African Americans with Early Rheumatoid Arthritis registry which serves to identify genetic and non-genetic prognostic factors of disease outcome using radiographic presence of bony erosions as the primary outcome measure (at 3 years disease duration). The registry will serve as the basis for prospective analyses of factors predictive of the clinical phenotype and outcomes. Four major academic medical centers in the southeast U.S. will gather data which will provide a resource for investigators interested in the genetics of RA in AA. The CLEAR registry will be utilized to examine the hypothesis that HLA-DR alleles and cytokine polymorphism in the tumor necrosis factor- alpha [TNF-alpha]/lymphotoxin (LT)- alpha, interleukin-1 (IL-1), and IL-6 loci, predict the presence or absence of erosion on hand and feet radiographs at 3 years disease duration in AA. The principal investigator, Dr. Larry Moreland, is a clinical researcher whose primary research interest has been the evaluation of biologic response modifiers (and their mechanisms) which are targeted at the disease process in rheumatoid arthritis.

TITLE: **A Model of Sjogren's Syndrome with Anti-RO/LA Antibodies** **NIAMS**
P.I.: **Robert H. Scofield, M.D.**
INSTITUTION: **Oklahoma Medical Research Foundation, Oklahoma City, OK**
GRANT NO.: **1R01AR47341-01**
KEYWORDS: **Sjogren's syndrome, autoimmune disease**
TYPE STUDY: **Basic**
AMOUNT: **$100,000**

Sjögren's syndrome (SS) is a common rheumatic autoimmune disease which initially affects the salivary and lacrimal glands but can effect the lungs, kidneys, central nervous system and vasculature. The etiology and pathological mechanisms are unknown for this disease and therapy is available but far from ideal. SS is an autoimmune disease as evidenced by the almost universal presence of autoantibodies in the sera of patients. The great majority of patients have antibodies binding one or more components of the Ro/La (or SSA/SSB) ribonucleoprotein particle, which is found in every mammalian cell type examined and whose function is not completely known. There are several animal models of SS but none of these models have high levels of anti-Ro or anti-La. Thus, while these models may prove useful for studying some aspects of the disease, insights into the origin and pathogenic potential of autoimmunity targeting the Ro ribonucleoprotein cannot be sought or found. The principle investigator has developed a new animal model of SS in which mice are immunized with short peptides (12 to 20 amino acids) derived from the sequence of the 60 kD Ro molecule. In some strains of mice the immune response expands with both B cell and T cell epitope spreading. Initially the immunogen peptide induces an immune reaction. Then other epitopes of the 60 kD Ro molecule are targeted as are epitopes on other molecules that are components of the Ro particle such as 52 kD Ro and La. In the SJL/J mouse strain pathology develops in the salivary gland that is similar to that found in humans with SS. This proposal will investigate this new model of disease that closely replicates its human counterpart. The nature of the cellular infiltrate will be studied as to its content of T and B lymphocytes and subsets. The cell type critical for development of disease will be determine by transfer experiments. Preliminary data indicate that the phenotype of helper T cells is critical to epitope spreading in this model. The relationships among immune response type, immune diversification after Ro-peptide immunization and development of pathology will be determined. Immunization will be carried out in mice deficient in various cytokines and with immune deviation strategies in order to determine whether immune deviation will alter development of epitope spreading and disease pathology.

TITLE: **Combining of N-of-1 Trials to Assess Fibromyalgia Therapies** **NIAMS**
P.I.: **Deborah R. Zucker, M.D.**
INSTITUTION: **New England Medical Center, Boston, MA**
GRANT NO.: **5R01AR045416-03**
KEYWORDS: **Fibromyalgia, autoimmunity**
TYPE STUDY: **Clinical**
AMOUNT: **$140,000**

Fibromyalgia is a common rheumatologic condition and treatment is a challenge. A recent study reported that combination therapy of amitriptyline and fluoxetine resulted in significantly greater improvement in patients' symptoms as compared with either drug alone. This project will use patient focused N-of-1 trials and combines these trials' results to obtain population estimates of treatment effectiveness. This will extend into community practice to enable comparison of center-based and practice-based results. This will also provide a methodological tool to obtain data from community physicians in practice-based settings.

TITLE: **Mechanisms of Lupus Induction in L-Canavanine** **NIEHS**
P.I.: **Patricia Fraser, Ph.D.**
INSTITUTION: **Center for Blood Research, Boston, MA**
GRANT NO.: **1R21ES10295-01**
KEYWORDS: **Systemic Lupus Erythematosus (SLE), estrogen receptors, androgen receptor, organochlorines, autoimmunity**
TYPE STUDY: **Clinical**
AMOUNT: **$100,000**

The sex difference in estrogen exposure may explain the sex imbalance in Systemic Lupus Erythematosus (SLE) risk. The specific aims of this proposal are to: 1) Determine androgen receptor (AR), estrogen receptor (ER), and cytochrome P450 genotypes in SLE subjects and controls by polymerase chain reaction based methodologies in a large SLE case/control study; and 2) Determine the relative importance of genetic markers in aim one with endogenous and exogenous estrogens and with exposure to organochlorines in predicting risk of SLE.

INFECTIOUS DISEASES/STD

TITLE: Mid-America Adolescent STD Cooperative Research Center **NIAID**
P.I.: Donald Orr, M.D.
INSTITUTION: Riley Hospital, Indianapolis, IN
GRANT NO.: 3U19AI043924-03S1A1
KEYWORDS: Infectious diseases, sexually transmitted diseases, prevention, behavior
TYPE STUDY: Clinical
AMOUNT: $50,000

Sexually transmitted diseases (STD) produce very serious outcomes in women, regardless of race, and often affect their infants as well. In addressing the racial health disparities in the occurrence of STD, NIAID supports Sexually Transmitted Diseases Cooperative Research Centers (STDCRCs), which provide a multi-disciplinary approach to research in the area of STD by bringing together basic science, clinical and epidemiological research, and behavioral intervention strategies for the prevention and control of STD.

MATERNAL- CHILD HEALTH

TITLE: Nursing Support Intervention for Mothers of Prematures **NINR**
P.I.: Diane Holditch-Davis, Ph.D.
INSTITUTION: University of Wisconsin-Madison, Madison, WI
GRANT NO.: 1R01NR05263-01A1
KEYWORDS: African American, rural, behavior, poverty, mental health
TYPE STUDY: Clinical
AMOUNT: $100,000

Premature infants are at risk for developmental problems, and Rural, African American prematures are at higher risk for these problems than other prematures. This health discrepancy is probably due to interactions among factors, such as poverty, barriers to service usage, the mothers' emotional distress from the infant's birth and hospitalization, and resultant parenting styles that may be less facilitative of infant development. The purpose of this study is to examine the effectiveness of a culturally congruent intervention providing support to rural, African American mothers of prematures from the time their infants are in intermediate care until they are 18 month of age. During phone calls and home visits, the intervention nurse will help mothers resolve emotional distress due to prematurity and reduce stress related to parenting in the context of work and family, support them in developing relationships with their infants, and help them identify acceptable resources and fit resources to her goals in order to meet complex infant health and developmental needs. The context for the intervention is a therapeutic relationship in which a culturally proficient nurse uses guided discovery to focus on the mother's experiences and concerns and help the mother to identify ways to reduce distress, improve parenting, and tap into strengths available in her family and culture. Mothers receiving the intervention and mothers receiving usual care will be compared to determine whether the intervention affects psychological well-being, mother-child relationship quality, length of use of child health and developmental surveillance services, and child development. The investigators expect that improvements in maternal psychological well-being will lead to longer use of services, better mother-child relationship quality, and better infant developmental status, particularly lessening the decrease in developmental status that is often seen after 12 months. The cost-effectiveness of the intervention will also be determined. Two hundred and twelve rural, African American mothers and their high-risk prematures will be recruited when the babies are in intermediate care and followed until they are 24 months corrected age. The mothers will be randomly assigned to control and intervention groups. The intervention will consist of an in-person contact in the hospital followed by a home visit 1-2 weeks after discharge and at 5, 10 and 15 months. Phone contacts will be made weekly during the first month, bimonthly for 2 months, and then monthly. Maternal psychological well-being will be measured using depressive symptoms, anxiety, posttraumatic stress symptoms, parenting stress, and minor daily stress. The quality of the infant's social environment will be measured using a 1-hour naturalistic observation of mother-infant interaction, the HOME Inventory, and two measures of maternal perception of the child. Length of use of services will be measured by the Child Services Survey and immunization status, a proxy for adequacy of well-child care, and confirmed from medical records. Child development will be measured by the Bayley II and a language assessment.

MENOPAUSE

TITLE: **Predicting Onset Age and Length of Menopausal Transition** **NIA**
P.I.: **Daniel M. Keenan, Ph.D.**
INSTITUTION: **University of Virginia, Charlottesville, VA**
GRANT NO.: **1K01AG19164-01**
KEYWORDS: **mathematical modeling of menopause, statistical predictors of timing of menopause, reproductive aging**
TYPE STUDY: **Clinical**
AMOUNT: **$100,558**

Because of the greater life expectancy of today, menopause and its physiological consequences are having an enormous impact on the well-being of the older female. The present research is concerned with identifying, elucidating, and quantifying the ovarian and neuroendocrine mechanisms underlying menopause. In particular, to establish that there is a specific sequential pattern of five phases that occurs during the menopausal transition, and to construct statistical predictors of the onset age and duration of the menopausal transition. Moreover, such a predictor will also allow for the estimation of a given subject's "hormonal-reproductive age", not chronological age, which has enormous implications for the infertility consequences of aging. For example, based upon certain endocrine reproductive measurements taken from say a given 40 year-old female, methods will be constructed by which to predict her age of perimenopause onset and its length, and at same time to state whether she is hormonally that of a 40 year-old, or more like a 45 or 35 year-old. The ability to predict the age and length of the menopausal transition is clinically important because early menopause has associated with it increased risk of cardiovascular disease and osteoporosis, whereas late menopause has associated with it an increased risk of breast cancer and endometrial cancer. This research consists of three components. First, five prospective and cross-sectional clinical studies specifically designed for the above aims will be conducted at the University of Virginia GCRC, using pre-, peri-, and postmenopausal subjects. Second, a biomathematical model for the aging hypothalamic-pituitary-ovarian axis will be developed which includes its several feedback/feedforward interactions, the dynamical onset and shutdown of the LH surge and ovulation, as well as its eventual cessation. Third, based upon the preceding two, hypotheses concerning the five phases will be tested, and predictors of onset age and duration constructed.

TITLE: **Study of Women's Health Across Nation II: (SWAN II)** **NIA**
P.I.: **Dr. Sonai McKinlay, Coordinating Center, Multiple sites and investigators plus a lab**
INSTITUTIONS: **New England Research Institute, Watertown, MA**
GRANT NO.: **2UO1AG12553-08**
KEYWORDS: **Menopause, aging, hormones, minorities, risk factors, disease**
TYPE STUDY: **Clinical**
AMOUNT: **$250,000**

SWAN consists of both cross sectional and longitudinal studies on the natural history of menopause and a characterization of endocrinology/physiology of premenopause. Five ethnic groups are included - Caucasian, African American, Hispanic, Chinese, and Japanese. There are 7 sites across the country - Boston, Pittsburgh, Chicago, Michigan, UCLA, UC Davis and New Jersey. For the cross-sectional study, there are approximately 16,000 women enrolled ranging in age from 40-55 years to determine the age of menopause. The longitudinal study has approximately 3150 women (450 at each site) between the ages of 42-52 to determine menopause-specific physiological changes and their predictors and the impact of menopause on subsequent disease. Measurements are being made of the major reproductive axis hormones (LH, FSH, estradiol, progesterone, and testosterone), adrenal markers of aging (DHEAs), other endocrine markers (TSH, sex hormone binding globulin [SHBG]) and new ovarian markers which have the potential to define the menopausal transition and the postmenopause.

TITLE: **Centers for Dietary Supplements Research: Botanicals** **NCCAM**
P.I.: **Norman Farnsworth, Ph.D.**
INSTITUTION: **University of Illinois at Chicago, IL**
GRANT NO.: **5P50AT00155-03**
KEYWORDS: **Botanicals, menopause, black cohosh, red clover, CAM**
TYPE STUDY: **Clinical and basic**
AMOUNT: **$100,000**

This multi-disciplinary team of investigators will focus on the study of the safety and efficacy of botanicals used to treat women for menopause. Studies will address mechanisms of action, identification of active compounds, and characterization of metabolism, bioavailability and pharmacokinetics of active species in these botanicals. The research component will consist of the following: 1) A pharmacognosy project to carry out standardization of botanical dietary supplements and structure elucidation of active compounds; 2) Isolate active compounds for structure elucidation, and then to determine the mechanism(s) of action of botanicals; 3) Study the metabolism, absorption and toxicity of active compounds in botanicals including immunotoxicity; and 4) Carry out phase I and II clinical trials of black cohosh (*Cimicifugai racemosa)* and red clover (*Trifolium pratense*).

TITLE: **Menopausal Transition, Mental Health and Ethnicity** **NIMH**
P.I.: **Joyce Bromberger, Ph.D.**
INSTITUTION: **University of Pittsburgh, Pittsburgh, PA**
GRANT NO.: **2R01MH59689-03A1**
KEYWORDS: **mood disorders, mental health, reproductive health, menopause, behavior**
TYPE STUDY: **Clinical**
AMOUNT: **$100,000**

This is an ancillary study of the Study of Women's Health Across the Nation (SWAN) in Pittsburgh. Our current sample consists of 412 African American and Caucasian women; aged 42-52 at the start of the study in 1996, who are beginning or will soon begin the menopausal transition. Women are interviewed annually with the Structured Clinical Interview (SCID) for DSM-IV Axis I Disorders. The specific aims are: 1) to assess whether women will be more likely to develop a new (recurrent) syndromal or subsyndromal depression during the perimenopausal transition than before or after, 2) to determine if a history of major depression (MDD) is a risk factor for the following during the transition; (a) syndromal or subsyndromal depression, (b) increased levels of perceived stress, somatic and psychological symptoms, or © decreased quality of life or functioning, and 3) to compare rates of new (recurrent) syndromal or subsyndromal depression across the transition for African American and Caucasian women. The longitudinal nature of the SWAN biological and psychosocial data (e.g., medical morbidity, stressful events, lifestyle behaviors) will allow us to evaluate these as antecedents, correlates, and consequences of depression during the course of the study. By continuing to collect systematically psychiatric data in our cohort in conjunction with the continued collection of Core SWAN data, we have unique opportunity to expand knowledge of women's mental health in midlife and beyond.

TITLE: **Menopausal Depression: Chronobiologic Basis** **NIMH**
P.I.: **Barbara L. Parry, M.D.**
INSTITUTION: **University of California, San Diego, La Jolla, CA**
GRANT NO.: **5R01MH059919-02**
KEYWORDS: **depression, menopause, hormone replacement therapy, behavior**
TYPE STUDY: **Clinical**
AMOUNT: **$100,000**

The specific focus of this project will be to examine the effects of estradiol and progesterone administration on circadian rhythms in humans. The subjects will be healthy postmenopausal women. The investigators will test the hypothesis that estrogen advances the phase and enhances the amplitude and synchrony (the stability of timing relationships) of biological rhythms as measured by melatonin, sleep and activity, whereas progesterone antagonizes these effects. This proposal represents an extension of the investigators' previous work that examined the effects of endogenous changes in estradiol and progesterone during the menstrual cycle on measures of mood and circadian rhythmicity. This work led to the development of new hypotheses and treatment strategies. The current proposal will allow investigation of these hypotheses further but in a more controlled design. The investigators anticipate gaining important information on possible mechanisms mediating the effects of reproductive hormones on mood and behavior and deriving relevant clinical treatment guidelines for menopausal women.

MENTAL HEALTH

TITLE: **Black Rural and Urban Caregivers Mental Health Functioning** **NIA**
P.I.: **Lethia Chadia, Ph.D.**
INSTITUTION: **Washington University, St Louis, MO**
GRANT NO.: **5R01AG15962-03**
KEYWORDS: **Mental health, caregivers, African American, rural, urban, aging**
TYPE STUDY: **Clinical**
AMOUNT: **$150,000**

This study will assess the mental health and social functioning of rural and urban African-American women who provide unpaid care to an elder (65 years and older) by using a cross-sectional research design and random sample of elders. This study will identify the type and quality of caregivers' formal and informal service use. Data will be obtained through personal interviews.

TITLE: **Relationship of Morbidity and Mortality Between Spouses** **NIA**
P.I.: **Nicholas Christakis, Ph.D.**
INSTITUTION: **The University of Chicago, Chicago, IL**
GRANT NO.: **1R01AG17548-01A2**
KEYWORDS: **morbidity, mortality, aging, spouses, widower effect, biodemography, health disparities**
TYPE STUDY: **Basic**
AMOUNT: **$380,000**

Employing the perspective and methods of the demography of again, the relationship between the morbidity and mortality of spouses will be examined. Questions about how the morbidity and mortality of one spouse, and the timing and nature of that morbidity and mortality, affects the morbidity, mortality, and timing and nature of morbidity and mortality in the other spouse will be asked. For example, is the hazard of death in one spouse (the "proband") increased by illness or death in the other spouse? If so, how does the proband's hazard of illness or death change over time after the onset of illness or death in the spouse? And how do these effects vary according to the type of severity or duration of the spouse's morbidity? Do particular illnesses in spouses place probands at particularly high risk of developing illness or dying themselves? What role do sociodemographic factors play in all these effects? To address these questions most effectively, a new panel data set with demographic, socioeconomic, and health information about one million elderly married couples followed up to ten years will be created. Using a variety of event history and fixed effects methods, four main analyses will be conducted. First, how morbidity in one spouse influences mortality in the other will be evaluated. Individuals married to unhealthy spouses will have worse mortality than those married to healthy spouses and that the longer the spouse is ill, the greater the effect is the working hypotheses. Certain types of spousal morbidity (e.g., those that most compromise activity levels) will be worse for probands is also hypothesized. Second, the widower effect (i.e., the increased tendency of the bereaved to die) with adjustment for the health of both spouses prior to widowhood will be evaluated; examine its temporal shape in detail; and assess its dependence on socioeconomic factors. Third, the principle investigator will evaluate how morbidity in one spouse influences morbidity in the other. Are healthy spouses better able than unhealthy spouses to provide health benefits in marriage? Fourth, the impact of widowhood on the morbidity, and not just mortality, of bereaved spouses will be evaluated. This work advances the demography of aging by: closely examining how an individual's morbidity and mortality are affected by the presence or absence of spousal support; focusing on cause-of-death specific aspects of demographic phenomena; examining theoretically interesting sub-populations along gender race, socioeconomic, and health status lines; and shedding light on the mechanisms of inter-spousal health effects. This work also has policy implications in that it: supports more accurate projections of the health burdens in the elderly, facilitates targeting of support services to the growing numbers of widowed elderly; and addresses important populations, such as minorities, the poor, the oldest old, those with dementia, and caregivers.

TITLE: **Depression Self-Management and Women with Disabilities** **NICHD**
P.I.: **Rosemary Hughes, Ph.D.**
INSTITUTION: **Baylor College of Medicine, Houston, TX**
GRANT NO.: **1R21HD40980-01**
KEYWORDS: **mental health, care-giving, health-related quality of life issues**
TYPE STUDY: **Clinical**
AMOUNT: **$173,882**

Depression is a common secondary condition associated with a primary disability. Disproportionately high among women compared to men, depression appears to be even more prevalent among women with disabilities. Although the risk for depression among all persons with disabilities appears to be higher than that among people in general, women with disabilities may be at even

greater risk compared to their male counterparts, yet the literature fails to report on a therapeutic modality that is responsive to the unique needs of depressed women with functional limitations. The purpose of this project is to develop and test an innovative, targeted, and theory-driven group intervention designed to ameliorate depression in women with physical disabilities. It is hypothesized that (a) women with disabilities who participate in a depression self-management group intervention will report lower levels of depression and higher levels of self-management of depression, self-efficacy, and social connectedness after the intervention and at a three-month followup, compared to those who participate in a depression education-only intervention; and, (b) self-management of depression, self-efficacy, and social connectedness will mediate the relation of disability to depression outcomes among women with physical disabilities. This study uses a randomized with-groups and between-groups pre/post-test design with a three-month follow-up. The intervention will be implemented at local public and private chronic care clinics with 154 women with physical disabilities who will randomly be assigned to participate in either the self-management intervention or education-only comparison workshop. The scores of the two groups on measures of self-management of depression, self-efficacy, social-connectedness, and depression will be compared. These assessments will be conducted at three time points, before and after the intervention period and at a three-month follow-up. Formative and summative evaluations, using qualitative and quantitative methodologies, will be conducted. This study is designed to be generalizable for clinical practice in physical medicine and rehabilitation, for mental health services for women with disabilities, and for public health policy governing the delivery of mental health services to people with disabilities.

TITLE: **Gender-Specific Risks for Depression in Adolescent Girls** **NIMH**
P.I.: **Sarah K. Bearman, B.A.**
INSTITUTION: **University of Texas at Austin, Austin, TX**
GRANT NO.: **5F31MH12834-02**
KEYWORDS: **mental health, adolescence, body image, eating disorders, prevention**
TYPE STUDY: **Clinical**
AMOUNT: **$25,076**

The proposed project is designed to examine a gender-specific model to explain the increased prevalence of depressive symptoms in adolescent girls compared to adolescent boys. Combining a longitudinal study which compares risk factors for depression in adolescent girls versus adolescent boys with a randomized prevention study of adolescent girls, this project would contribute significantly to the literature concerning both gender differences in rates of depression and prevention programs for depression in adolescent girls. Aim 1 is to test whether body imaging and eating disturbances, hypothesized to be gender-specific risk factors, emerge as prospective predictors of depressive symptoms in females, and whether this partially accounts for the relation between gender and depression. Aim 2 is to test whether a randomized experiment that reduced body dissatisfaction will lead to a subsequent decline of depressive symptoms in adolescent females, and whether manipulating body dissatisfaction will impact dieting and bulimic pathology. The aims for these two studies will be addressed through examination of prospective data from a community sample of adolescents (N=400) and a randomized experiment of a high-risk sample of adolescent females (N=60), respectively.

TITLE: **Effects on Children of Treating Maternal Depression** **NIMH**
P.I.: **Anne Riley, Ph.D.**
INSTITUTION: **Johns Hopkins University, Baltimore, MD**
GRANT NO.: **5R01MH058384-04**
KEYWORDS: **Mental health, maternal depression, children, environment, behavior**
TYPE STUDY: **Clinical**
AMOUNT: **$50,000**

Maternal depression has devastating effects on the mental and physical health of children. This project will study the influence of treating maternal depression on children ages 5-11. This project will study 150 elementary-school aged children whose mothers are depressed (50 Hispanic, 50 African American and 50 Caucasian) and 50 comparable children whose mothers are not depressed. Their mental health and functioning will be assessed by natural raters in their environments over a two-year time period that will link child functioning, symptomatology, and psychiatric disorders to mothers' symptomatology, parenting behavior, and family environment.

TITLE: **Sex Differences in Self-Evaluation: Social Factors** **NIMH**
P.I.: **Eva Pomerantz, Ph.D.**
INSTITUTION: **University of Illinois, Champaign, IL**
GRANT NO.: **5R01MH057505-03**
KEYWORDS: **Gender socialization, self-evaluation, depression, mental health, behavior**
TYPE STUDY: **Clinical**
AMOUNT: **$38,684**

Girls are more likely than boys to possess self-evaluative mechanisms that may heighten vulnerability to depressive and anxiety symptoms. It is hypothesized that culturally held gender stereotypes may cause parents to be more controlling in certain behavioral domains with girls than with boys. This pattern of gender socialization is expected to lead girls to be more likely than boys to possess self-evaluative mechanisms that heighten vulnerability to depressive and anxiety symptoms.

MUSCULOSKELETAL SYSTEMS

TITLE: **Doxycycline Effect on Osteoarthritis Progression** **NIAMS**
P.I.: **Kenneth Brandt, MD**
INSTITUTION: **Indiana University School of Medicine, Indianapolis, IN**
GRANT NO.: **5R01AR43348-05**
KEYWORDS: **Osteoarthritis, doxycycline**
TYPE STUDY: **Clinical**
AMOUNT: **$200,000**

Osteoarthritis (OA) of the knee is the most common cause of chronic disability in this country. This group has shown that prophylactic oral administration of doxycycline (doxy) markedly reduces the severity of cartilage damage in a canine model of OA; even when therapy was initiated after cartilage lesions were established, a protective effect was apparent. Similar results have been noted in guinea pig and rabbit models of OA. The effect is associated with reduction in the levels of collagenase and gelatinase in the OA cartilage. Based on the encouraging data in animal models of OA, a randomized-placebo-controlled 30-month clinical trial will examine the effect of this drug and its ability to prevent the progression of early knee osteoarthritis in women.

TITLE: **Glucocorticoids Alter the Birth and Death of Osteoblasts** **NIAMS**
P.I.: **Robert Weinstein, Ph.D.**
INSTITUTION: **University of Arkansas for Medical Sciences, Little Rock, AR**
GRANT NO.: **5RO1AR 46191-03**
KEYWORDS: **Glucocorticoids, osteoblasts, parathyroid hormone, osteoporosis**
TYPE STUDY: **Clinical and basic**
AMOUNT: **$100,000**

This study will characterize the effects of chronic glucocorticoid excess on several aspects of bone physiology. Patients with glucocorticoid-induced bone loss will be included. The effect of alendronate (Fosamax) and parathyroid hormone will be tested in mice for efficacy in ameliorating the effect of glucocorticoids.

TITLE: **Low-Dose Doxycline Effects on Osteopenic Bone Loss** **NIDCR**
P.I.: **Jeffrey B. Payne, DDS**
INSTITUTION: **University of Nebraska, Lincoln, NE**
GRANT NO.: **1R01DE12872-01A2**
KEYWORDS: **clinical trials, periodontitis, osteoporosis**
TYPE STUDY: **Translational, Clinical**
AMOUNT: **$363,768**

This study seeks to demonstrate the clinical efficacy of low dose doxycycline (LDD) therapy in reducing bone loss due to periodontitis and estrogen deficiency in a postmenopausal estrogen deficient osteopenic population. Success in reducing or arresting bone loss related to periodontitis in an estrogen deficient osteopenic group would represent important progress in understanding and managing the pathophysiologic mechanisms that are involved in bone loss with this process.

NEUROLOGY

TITLE: Estrogen Induced Hippocampal Seizure Susceptibility — **NINDS**
P.I.: Catherine Woolley, Ph.D.
INSTITUTION: Northwestern University, Evanston, IL
GRANT NO.: 5R29NS037324-04
KEYWORDS: Epilepsy, hippocampus, estradiol, neurosciences research
TYPE STUDY: Basic
AMOUNT: $35,000

A significant proportion of women with epilepsy experience increased seizure frequency during phases of the menstrual cycle in which estradiol levels are elevated. This is termed catamenial epilepsy. Animal models of epilepsy also demonstrate that estradiol increases seizure susceptibility. Previous work in the adult female rat has shown that estradiol induces new dendritic spines and axospinous synapses on CA1 pyramidal cells in the hippocampus, a key brain structure in the generation and propagation of seizure activity. Furthermore, estradiol-induced dendritic spines and synapses are correlated with increased excitability of hippocampal neurons and decreased hippocampal seizure threshold. This correlation suggests that estradiol-induced seizure susceptibility in women with catamenial epilepsy may be due, at least in part, to hormone-mediated alterations in hippocampal synaptic connectivity. The studies in this proposal will use the adult female rat to test the hypothesis that estradiol facilitates seizure activity through alteration of hippocampal synaptic structure and physiology.

NUTRITION

TITLE: Food Choline Database Project — **NHLBI**
P.I.: John H. Himes, Ph.D.
INSTITUTION: University of Minnesota Twin Cities, Minneapolis, MN
GRANT NO.: 5U24HL61778-04
KEYWORDS: nutrition, nutrient analysis database, choline metabolism
TYPE STUDY: applied - National database
AMOUNT: $50,000

The purpose of this program is to develop a comprehensive and high-quality database on the choline content of foods commonly eaten in the United States. The data will be generated by analyzing nationally representative samples of 400 foods for their content of various forms of choline. Research activities will be managed by the US Department of Agriculture as a dovetailed component of the ongoing National Food and Nutrient Analysis Program, which has already collected the needed food samples. The total direct cost for developing the database is estimated at $400,000 (400 foods at $1000/food). The food choline database - resulting from this project will rectify serious gaps in the general knowledge of choline metabolism and requirements, which require calculating individual and population level estimates of choline intake.

TITLE: Altered Calcium and Vitamin D Metabolism in PMDD — **NIDDK**
P.I.: Susan Thys-Jacobs, M.D.
INSTITUTION: St. Luke's-Roosevelt Hospital Center, New York, NY
GRANT NO.: 1R01DK57869-01
KEYWORDS: PMDD, nutrition
TYPE STUDY: Clinical
AMOUNT: $100,000

Premenstrual Dysphoric Disorder (PMDD) is widely recognized as a recurrent disorder related to hormone variations of the menstrual cycle. Whereas alterations in calcium homeostasis have long been associated with many affective disturbances, recent evidence has suggested that luteal phase symptomatology may be associated with a perturbation in calcium homeostasis. The purpose of this investigation is to understand more completely the extent to which calcium regulation is disturbed in PMDD by utilizing new tools to access calcium and bone turnover. The long term objective is to elucidate the pathophysiology of PMDD as it relates to the calciotropic hormones and bone markers. The experimental design involves enrolling 70 with PMDD and 35 controls. Following two months of baseline symptom documentation, women with PMDD and controls with be enrolled in a nine month observational period with frequent hormonal samplings, urinary collections and daily ratings. Understanding the pathophysiology associated with PMDD may lead to effective therapeutic strategies to prevent the neuropsychiatric disturbances and abnormal calcium regulation that are characteristic of this disorder.

OBESITY/OVERWEIGHT

TITLE: Study of Health Outcomes of Weight Loss (SHOW) **NIDDK**
KEYWORDS: Type 2 diabetes, obesity, cardiovascular, cerebrovascular, neurosciences research, behavior
TYPE STUDY: Clinical
AMOUNT: $100,000

Multiple centers are participating in a randomized, controlled, multi-center clinical trial in obese type 2 diabetic patients. This trial will examine the effects of interventions designed to produce sustained weight loss and a range of health outcomes. The primary outcome is anticipated to be differences in progression of atherosclerosis. This study will examine the effects of the interventions on cardiovascular and cerebrovascular event rates, cardiovascular and all-cause mortality, cardiovascular risk factors, glycemic control, and other outcomes. There will be three arms: 1) Community Care-The primary care physician will be given standard of care recommendations for treatment of obesity and comorbid conditions such as diabetes; 2) Intensive Lifestyle Intervention - Patients will undergo a long-term behavioral treatment program that includes dietary modification, increased physical activity, and behavioral therapies designed to enhance weight loss and weight maintenance. Obesity related comorbid conditions will be treated as in group 1; 3) Intensive Lifestyle Intervention plus Weight Loss Medication - Medication will be added to the intensive lifestyle intervention in an attempt to enhance long-term weight maintenance. Comorbid conditions will be treated as in group 1.

TITLE: A Mentor-Based Approach to Long Term Weight Loss **NIDDK**
P.I.: John M Jackicic, Ph.D.
INSTITUTION: The University of Kansas Center for Research, Lawrence, KS
GRANT NO.: 5R01DK058002-03
KEYWORDS: Obesity, prevention, behavior
TYPE STUDY: Clinical
AMOUNT: $20,000

The primary goal of this study is to examine the effect of a mentor-based intervention on long-term weight loss in overweight adult women. The primary analysis will focus on the effect of this intervention on long-term weight loss in women receiving a mentor-based intervention, with additional analysis focusing on the effect of this intervention on long-term weight loss in women functioning as mentors in this study. The investigators hypothesize that a mentor-based intervention will improve long-term weight loss in both mentors and mentor-recipients compared to individuals receiving a standard non-mentored-based weight loss intervention. It is believed that a mentor-based intervention will lead to improvements in the long-term treatment of obesity.

TITLE: Internet-Aided Prevention of Pregnancy-Induced Obesity **NIDDK**
P.I.: Jennifer Lovejoy, Ph.D.
INSTITUTION: Pennington Biomedical Research Center, Baton Rouge, LA
GRANT NO.: 5R01DK57446-02
KEYWORDS: Pregnancy, obesity, African American, behavior
TYPE STUDY: Clinical
AMOUNT: $20,000

This application targets the prevention of pregnancy-associated obesity in African-American women. The overall goal of this proposal is to evaluate the effectiveness of traditional vs. Internet-aided behavior modification for weight management in postpartum African-American women. The Internet-based intervention will be used in face-to-face group sessions to allow for more extensive behavioral feedback. The research will address the primary hypothesis that the use of the Internet-aided behavioral intervention will be more effective than traditional behavioral intervention programs in preventing excess postpartum weight retention.

TITLE: Primary Care Office Management of Obesity **NIDDK**
P.I.: Pamela Davis Martin, Ph.D.
INSTITUTION: Pennington Biomedical Research Center, Baton Rouge, LA
GRANT NO.: 5R01DK57476-03
KEYWORDS: Obesity, African-American, patient-centered intervention, behavior
TYPE STUDY: Clinical
AMOUNT: $20,000

This randomized, two-arm treatment study will use culturally sensitive educational materials by trained primary care physicians. It will compare physician-directed education (standard care group) to another group who receive customized education plus patient-centered messages by primary care physicians. It will attempt to determine whether a physician-delivered patient-centered intervention is more effective than standard care in regard to prevention of weight gain and achievement of weight loss at six months. It will also examine whether the groups differ in regard to weight maintenance at 12 and 18 months follow-ups. It is hypothesized that patients in the patient-centered group will demonstrate less weight gain, more weight loss at six months, greater maintenance of weight loss at 12 and 18 months as well as dietary and physical activity improvement throughout the observation period than patients receiving standard care.

TITLE: **Weight Gain in Pregnancy: Staying the Range** **NIDDK**
P.I.: **Christine Olson, Ph.D.**
INSTITUTION: **Cornell University, Ithaca, NY**
GRANT NO.: **5R01DK57439-02**
KEYWORDS: **Pregnancy, obesity, prevention**
TYPE STUDY: **Clinical**
AMOUNT: **$20,000**

The proposed project focuses on primary prevention of obesity in women by slowing the accumulation of weight in the childbearing years. The long-term goal of the proposed study is to decrease the amount of weight retained in the postpartum period by lower income, rural white women who enter pregnancy with normal or high body mass indices. This goal will be addressed by encouraging women to gain an amount of weight during pregnancy that is within the appropriate ranges recommended by the Institute of Medicine (IOM). The project specifically aims to decrease by 50% the proportion of women who gain above the upper limit of the appropriate IOM range. The project will be implemented in a primary health care setting. The study has a prospective cohort design with an historical control group.

TITLE: **Weight Control in Peri- and Early Postmenopausal Women** **NIDDK**
P.I.: **Susan Racette, Ph.D.**
INSTITUTION: **Washington University, St. Louis, MO**
GRANT NO.: **1R01DK5746-01**
KEYWORDS: **Obesity, perimenopausal, postmenopausal, prevention, behavior**
TYPE STUDY: **Clinical**
AMOUNT: **$20,000**

The primary aim of this study is to assess the effectiveness of a modest lifestyle intervention program on preventing gains in body weight, whole body fat mass, and abdominal adipose tissue during a 2-year period in perimenopausal and early postmenopausal women who are at risk for obesity. The second aim is to determine the effects of the intervention on daily physical activity, which will be calculated from total daily energy expenditure and resting metabolic rate, as determined by the doubly labeled water method and indirect calorimetry, respectively. A randomized, controlled trial will be used to evaluate the intervention in female employees of a large Midwestern medical center.

TITLE: **Clinical and Experimental Study of Human Obesity** **NIDDK**
P.I.: **Albert Stunkard, M.D.**
INSTITUTION: **University of Pennsylvania, Philadelphia, PA**
GRANT NO.: **5RO1DK56251-05**
KEYWORDS: **Eating disorders, obesity, mental health**
TYPE STUDY: **Clinical**
AMOUNT: **$100,000**

This project is a longitudinal study of 78 children, from 3-5 years of age, from either obese or non-obese mothers. The goal is to examine a group of variables related to food intake and energy expenditure along with measures of body size or composition, utilizing not only weight and length but measures of skinfold thickness and percent fat by dual energy x-ray absorptiometry and body water, and isotope dilution measures. The study has already found that the two independent measures of energy intake at three months of age predict body size and composition at one year of age and discounted the belief that a low total energy expenditure and maternal obesity predict body size and composition at one year of age. This study will continue to search for risk factors for obesity in the early childhood years.

PAIN

TITLE: Low Back Pain - A Multi-Center Randomized Trial — **NIAMS**
P.I.: James Weinstein, DO
INSTITUTION: Dartmouth Medical School, Hanover, NH
GRANT NO.: 5U01AR045444-03
KEYWORDS: Neurosciences research, back pain
TYPE STUDY: Clinical
AMOUNT: $100,000

Low back pain is considered one of the most widely experienced health problems. Rates of spinal surgery have increased sharply over time and 15-fold geographic variation in rates of these surgeries has been documented. There is little evidence proving the effectiveness/efficacy of these surgical therapies over non-operative management. This study will use the resource of the National Spine Network to conduct multi-centered, randomized, controlled trials for three common diagnostic groups - lumbar intervertebral disc herniation (IDH), spinal stenosis (SpS) and spinal stenosis secondary to degenerative spondylolithesis (DS). The trials will compare the most commonly used standard surgical treatments to the most commonly used standard non-operative treatments. The primary endpoints will be changes in general health-related quality of life as measured by the SF-36 health status questionnaire and spine-related disability as measured by the Oswestry Low Back Pain questionnaire. Secondary endpoints will include patient satisfaction with treatment, resource utilization of estimation of cost, and utility for current health for estimation of quality adjusted life years.

TITLE: Pain Management in Temporomandibular Joint Disorders — **NIDCR**
P.I.: Jennifer Haythornthwaite, Ph.D.
INSTITUTION: Johns Hopkins University, Baltimore, MD
GRANT NO.: 1R01DE13906-01A1
KEYWORDS: TMD, pain control, behavioral interventions, neurosciences research
TYPE STUDY: Behavioral
AMOUNT: $263,058

The primary goal of the proposed project is to test the efficacy of psychological interventions, a pharmacological intervention, and the combination of these interventions in reducing pain and improving function in persons with temporomandibular disorders (TMD). Since psychological interventions are costly and require expertise that is frequently unavailable in primary care settings, the proposed project will also examine the efficacy of a minimal contact/self help psychological intervention based on cognitive-behavioral therapy for pain management. In addition to examining the separate and combined effects of psychological and pharmacological interventions for TMD pain, the proposed study will examine whether the minimal contact cognitive-behavioral intervention can accomplish comparable reductions in pain and improvements in function relative to the therapist-administered treatment.

TITLE: Trigeminal Pain Mechanisms and Control — **NIDCR**
P.I.: Jon D. Levine, Ph.D.
INSTITUTION: University of California at San Francisco, San Francisco, CA
GRANT NO.: 2P01DE08973-11A1
KEYWORDS: pain control mechanism, orofacial neuropathies, neurosciences research
TYPE STUDY: Basic
AMOUNT: $151,174

The chemotherapeutic agent paclitaxel(Taxol) is widely used for the treatment of many different types of carcinomas. At present, the dose of paclitaxel that can be tolerated by patients is limited primarily by the development of a painful peripheral neuropathy characterized by parenthesis, myalgia and arthralgia. Similar dose-limiting painful neuropathies are produced by other microtubule-disrupting chemotherapeutic drugs, including vincristine. Therefore, amelioration of the neuropathic pain might not only reduce the suffering of patients who receive paclitaxel or vincristine therapy, but also increase the effectiveness of their treatment by permitting the use of higher doses of the drugs. We propose a series of experiments to elucidate the cellular mechanisms of paclitaxel-induced painful peripheral neuropathy in the rat. By improving our understanding of the cellular mechanisms of neuropathic pain, these studies can potentially provide important insights into the pathophysiology and treatment of orofacial neuropathies.

TITLE: **Uterine Pain - Mechanisms and Modulation** **NINDS**
P.I.: **Ursula Wesselmann, M.D.**
INSTITUTION: **Johns Hopkins University, Baltimore MD**
GRANT NO.: **5RO1NS036553-04**
KEYWORDS: **Chronic pain, neurobiology, neurosciences research**
TYPE STUDY: **Basic**
AMOUNT: **$100,000**

These studies will provide fundamental new information about the neuroanatomical and neurophysiological mechanisms of pelvic and uterine pain. An experimental model of uterine pain will be used to obtain information about the spinal pathways that process nociceptive afferent input from the uterus; assess the effects of peripheral opioid application on the spinal processing of nociceptive inputs from the uterus; and to determine the influence of the estrous cycle on spinal cord processing of noxious uterine stimulation.

PHARMACOLOGY

TITLE: **Gender and Risk of Drug-Induced Cardiac Arrhythmias** **NHLBI**
P.I.: **Ray Woosley, MD, Ph.D.**
INSTITUTION: **Georgetown University, Washington, DC**
GRANT NO.: **5R01HL58743-02**
KEYWORDS: **drug-induced arrhythmias, gender differences, cardiovascular research**
TYPE STUDY: **Clinical**
AMOUNT: **$50,000**

This study will test the hypothesis that gender-specific differences in cardiac ion current densities are responsible for the observed gender differences in QT interval length and the greater sensitivity of females to drugs that cause QT lengthening. They will use the rabbit model system to identify gender-related differences in cardiac electrophysiological characteristics (action potential and whole cell patch clamp recordings at baseline and after quinidine or d-sortalol) and identify the ionic basis for these differences in rabbit ventricular muscle. They will also evaluate the potential roles for sex steroid hormones in the regulation of specific ion channels that display gender differences at baseline or in response to drugs.

TITLE: **Endogenous Regulators of Drug Metabolism** **NIGMS**
P.I.: **Bernard H. Shapiro, Ph.D.**
INSTITUTION: **University of Pennsylvania, Philadelphia, PA**
GRANT NO.: **2R01GM45758-09**
KEYWORDS: **signal transduction, women's health, pharmacology**
TYPE STUDY: **Basic**
AMOUNT: **$317,000**

The broad objective of this proposal is to investigate the mechanisms by which growth hormone (GH) regulates the sexually dimorphic expression of hepatic isoforms of cytochrome P450 (CYP), which impacts on concerns regarding the gender-effectiveness of therapeutic agents. Having identified the basic elements in the masculine "episodic" and feminine "continuous" plasma GH profiles that selectively "signal" the express of 8 constitutive sex-dependent rat CYPs, we now propose to examine the mechanisms by which the hepatocyte discriminates between the numerous GH signals and transduces their messages to the nucleus. The investigators hypothesize that each extracellular signal in the circulating GH profiles activate a different signal transduction pathway responsible for the induction or suppression of each isoform. The investigators propose to identify the different signal transduction pathways mediating GH regulation of CYPs by both infusing GH-devoid rats and exposing primary rat hepatocytes to individual GH signals known to regulate expression of each CYP isoform. Similar experiments will be conducted to identify GH-dependent CYP isoforms in human hepatocytes and the signal transduction pathways mediating their action. Expression levels of hepatic CYPs are gender-dependent in the adult rat (as well as in every other species examined), and regardless of the treatment, males cannot be induced to express the full female pattern of hepatic CYPs nor can females be treated to express normal male patterns. The investigators propose to study whether the sexually dimorphic CYP isoforms are permanently imprinted by determining the degree of CYP sex reversal in gender crossed (male or female and female to male) hepatocyte transplants. Follow-up studies will examine gender-based imprinting differences in the signal transduction responses to GH signals.

PHYSICAL ACTIVITY

TITLE: African American Women's Response to Physical Activity — **NINR**
P.I.: Beth A. Staffileno, DNSC
INSTITUTION: Rush-Presbyterian St. Luke's Medical Center, Chicago, IL
GRANT NO.: 1K23NR00168-01A1
KEYWORDS: minority women, poverty, cardiovascular research, prevention hypertension, obesity
TYPE STUDY: Clinical
AMOUNT: $98,993

The immediate goal of this 3-year proposal is to strengthen the candidate's research knowledge and skills and provide an opportunity to synthesize these in the investigations of physical activity and other outcomes as they relate to cardiovascular disease control and prevention in women, especially those of ethnic minorities. The overall goal is to produce an independent investigator whose career commitment is to the production and dissemination of science that will make an impact on the health of minority women. To reach this goal, the candidate will pursue a 3-phase program, based on a Research Essentials model, the review of which by the trainee and her co-mentors produced 9 training objectives. These objectives provide for progression from knowledge acquisition to skill development to synthesis. Rush University is an environment conducive to multidisciplinary biomedical and clinical research projects. Two mentors with expertise in patient-oriented outcomes and cardiovascular research (from the colleges of nursing and medicine, respectively) will oversee the candidate's training and execution of the research project. In addition, 3 senior researchers and content experts, in the areas of recruitment and retention in women and minority populations and patient-oriented outcomes, will serve as consultant faculty. This proposed research synthesis study uses a randomized, controlled design to investigate the impact of short bouts of accumulated physical activity on blood pressure (BP) and health-related quality of life in African American women, a high-risk group for hypertension. This study will not only quantify the impact of exercise prescription on BP and quality of life, but also, for the first time, investigate the role of endothelial function and hemodynamic correlates of BP change in this high-risk population. Given the well documented high prevalence of obesity in African American women, the low levels of physical activity and fitness in these same women, and the link between physical activity/fitness, and obesity with elevated BP, hypertension-prone and mildly hypertensive African American women are logical targets for a physical activity intervention. Findings from this project as well as the knowledge and skills developed as part of the training experience, will enable the candidate to propose an R01 level investigation, (as the principle investigator, in multidisciplinary patient-oriented research.)

PULMONOLOGY

TITLE: LAM Patient Registry — **NHLBI**
P.I.: Gerald, Beck Ph.D.
INSTITUTION: Cleveland Clinic Foundation, OH
GRANT NO.: 5U01HL58440-05
KEYWORDS: Lymphangioleiomyomatosis, pulmonary disease, registry, women's health
TYPE STUDY: Clinical
AMOUNT: $100,000

Lymphangioleiomyomatosis (LAM) is a rare but fatal pulmonary disease of unknown etiology that strikes women, primarily in their reproductive years. The goal of this project is to establish a registry of individuals with LAM by forming a consortium of six clinical centers and referring physicians who treat patients with LAM. The cohort of identified individuals with LAM will be used to characterize the clinical features of subjects and provide information on the natural course of the disease. The registry will include clinical data and tissue samples which will be used to study the course of the disease and assess interventions. Data and tissue samples will also be banked for future studies.

REPRODUCTIVE HEALTH/DEVELOPMENTAL BIOLOGY

TITLE: **Evidence Report - Use of Uterine Artery Embolization (UAE) Procedures and Related Surgical Procedures for Treatment of Conditions That Can Lead to Hysterectomy** **AHRQ**
KEYWORDS: **uterine fibroids, surgical options, hysterectomy and alternative treatments, women's health**
TYPE STUDY: **Collaborative Federal Agency Review**
AMOUNT: **$200,000**

ORWH and The Agency for Healthcare Research and Quality (AHRQ) will develop an evidence report on uterine artery embolization procedures and related surgical procedures for treatment of conditions that can lead to hysterectomy. The NIH/ORWH will work with AHRQ to provide guidance, as appropriate to the Evidence-based Practice Centers (EPCs) conducting this review. The EPCs review all relevant scientific literature on assigned clinical care topics and produce evidence reports.

TITLE: **Aging of Brain: Effects of Prenatal Nutrition** **NIA**
P.I.: **Jan Blusztajn, Ph.D.**
INSTITUTION: **Boston University, MA**
GRANT NO.: **2PO1AG09525 -08**
KEYWORDS: **Prenatal nutrition, choline, folic acid, nutrition, neurosciences research, aging**
TYPE STUDY: **Basic**
AMOUNT: **$100,000**

The goal of this study is to determine the mechanisms by which the availability of choline and folic acid during the prenatal period modifies brain structure and function in development, adulthood and old age. The proposed studies will 1) determine the molecular mechanisms involved in the brain reorganization that is governed by choline and folate availability by studying signal transduction pathways and developmental patterns of gene expression in brain; 2) measure synaptic function and plasticity in hippocampus of rats exposed to varying levels of choline or folate in utero; 3) examine age-related changes in conditioned stimulus processing (attention) as a function of the prenatal availability of choline and folate; 4) determine if supplementation with folate in early development leads to lifelong changes in spatial memory, brain anatomy and neurochemistry; 5) investigate whether choline supplementation either prenatally or across the lifespan ameliorates behavioral, anatomical, and biochemical deficits seen in mice lacking the apolipoprotiein E.

TITLE: **Development and Differentiation in Reproductive Axis Cooperative Reproductive Sciences Research at Minority I institutions RFA** **NICHD**
P.I.: **Director–David R. Mann, Ph.D., Morehouse School of Medicine, Atlanta, Ga**
Co-director/Partner–Tony M. Plant, Ph.D., University of Pittsburgh, Specialized Cooperative Centers Programs in Reproductive Research , Pittsburgh, PA
GRANT NO.: **1-54HD-41749-01**
KEYWORDS: **reproductive, minority institutions, developmental neurobiology, apoptosis, gene expression, biological model, cell growth regulation**
TYPE STUDY: **Basic science, translational, clinical**
AMOUNT: **$250,000**

The purpose of this initiative is to form a cooperative program that will augment and strengthen the research infrastructure and research capabilities of faculty, students, and fellows at minority institutions by supporting the development of new, and/or the enhancement of ongoing, basic science, translational, and clinical research that focuses on topics deemed to be of high priority and significance because of their critical importance to reproductive health.

The Morehouse Reproductive Science Research Center consists of four research projects and an administrative core. Grant No. 1U54HD41749-01 (Development and Differentiation in Reproductive Axis), David R. Mann, is the parent grant. Grant No. 1–1U54HD41749-010001 (Hypothalamic GnRH Pulse Generator), David R. Mann. Grant No. 2--1U54HD41749-010002 (Role of Prohibitin in Follicular Development), Winston E. Thompson. Grant No. 3--1U54HD41749-010003 (Role of GnRH In Luteolysis), Rajagopala Sridaran. Grant No. 4--1U54HD41749-010004(SP Regulation of Gene Expression in Spermatogenesis), Kelwyn H. Thomas.

TITLE: **Fragile X Mental Retardation Gene Premutation** **NICHD**
P.I.: **Pamela L. Mellon, Ph.D.**
INSTITUTION: **University of California San Diego, La Jolla, CA**
GRANT NO.: **5U54HD12303-22**
KEYWORDS: **premature ovarian failure, genetics, women's health**
TYPE STUDY: **Translational**
AMOUNT: **$113,000**

Fragile X syndrome (FRX) is one of the most frequent forms of congenital mental retardation in humans, usually resulting from lack of expression of the Fragile X Mental Retardation Gene (FMR1). Interestingly, unaffected carriers or so-called FRX premutation carriers show an increased prevalence of Premature Ovarian Failure (POF) which is generally defined as cessation of reproductive function by age 40. While it is estimated that 1% of women worldwide experience POF, the prevalence of POF in FRX premutation carriers has been reported to be 16%. On a more basic science level, the FMR1 gene is expressed in many tissues, but its function is unknown. In both male and female gonads, the gene is expressed in the germ cells. For the ovary, expression of the FMR1 gene in oogonia and oocytes could have profound implications for the regulation of oocyte number and ovarian follicular reserve which clearly can impact the cessation of reproductive function.

Three aims are proposed to: 1) characterize the cell-specific FMR1 gene expression changes in normal human and mouse ovaries through their respective reproductive cycles; 2) define the physiology of hypothalamic-pituitary-ovarian function in human female FRX premutation carriers; and 3) create a repository of genetic material and extensive phenotypic information about women with POF that could eventually be used to test other candidate genes for POF.

TITLE: **Neuroimmunology/Cytokine Alterations in Vulvodynia** **NICHD**
P.I.: **Barbara D. Reed, Ph.D.**
INSTITUTION: **University of Michigan at Ann Arbor, Ann Arbor, MI**
GRANT NO.: **5R01HD040112-02**
KEYWORDS: **women's health, chronic pain, vulvodynia, clinical research**
TYPE STUDY: **Clinical**
AMOUNT: **$180,954**

Hundreds of thousands of women in the United States suffer from vulvodynia a chronic burning vulvar pain of unknown cause. Millions of health care dollars are spent annually for this disorder in the United States alone, not only on management, but also on the large proportion of cases that are misdiagnosed and inadequately treated. This pain, associated with allodynia and hyperpathia, has a strong genetic predelection, with African-American women rarely being affected. The broad, long-term objectives of this proposal are to assess the differences in specific neuroimmunological characteristics between women with vulvodynia and asymptomatic controls. The specific aims include: evaluation of 1) the individual cytokine/neurokine production response to stimulation of peripheral blood; 2) local changes in nerve fiber, mast cell, Substance P and serotonin density in vulvar tissue; 3) the interactions of the systemic and local immunologic systems assessed in 1) and 2); and 4) the multivariable assessment of these laboratory factors with historical risk factors for vulvodynia to explore potential pathophysiologic mechanisms accounting for the historical risk factors identified. The research design involves a case-control evaluation of 100 women with vulvodynia, 100 controls matched for ethnicity, and 100 African-American control women, using questionnaires, physical examinations, clinical laboratory data, cytokine/neurokine levels in stimulated peripheral blood, and neuroimmunhistological assessment of vulvar, biopsy specimens for nerve fiber density, mast cells, Substance P and serotonin. Results from this study will lead to improved understanding of neuroimmunologic alterations in women with vulvodynia which will direct future therapeutic strategies for this disorder.

TITLE: **Mechanism of Vulvodynia** **NICHD**
P.I.: **Ursula Wesselmann, Ph.D.**
INSTITUTION: **John Hopkins University, Baltimore, MD**
GRANT NO.: **1R01HD039699-01A1**
KEYWORDS: **women's health, chronic pain, neurophysiology**
TYPE STUDY: **Clinical**
AMOUNT: **$19,046**

The long range objective of this research is to elucidate the pathophysiological mechanisms of vulvodynia, a chronic pain syndrome of the vaginal and vulvar area, in order to develop improved treatment strategies for alleviating chronic pain in these women, targeted at the underlying pathophysiological mechanism. We propose two approaches to gain better understanding of the

pathophysiological mechanisms of vulvodynia: (1) We will develop an animal model in the rat, that will allow to study the spinal cord pathways involved in the processing of noxious input from the vagina. (2) We propose to characterize pain in patients with vulvodynia in detail. Out hypothesis is that patients with vulvodynia can be differentiated into distinct groups based on their pain characteristics, and that treatment of pain in vulvodynia will be more effective, if based on recognition of the underlying neurophysiological mechanisms.

TITLE: **Maternal Peridontitis and Adverse Pregnancy Outcome** **NIDCR**
P.I.: **Waranuch Pitiphat, M.S.**
INSTITUTION: **Harvard School of Dental Medicine, Boston, MA**
GRANT NO.: **1R03DE14004-01A1**
KEYWORDS: **adverse pregnancy outcomes, periodontitis, women's health**
TYPE STUDY: **Case-Control Study**
AMOUNT: **$25,000**

This study will evaluate whether periodontitis is a risk factor for adverse pregnancy outcomes, by adding an oral component to the ongoing Project Viva, a prospective study of 6,000 pregnant women, to evaluate this association. Maternal infection during pregnancy has been demonstrated to play an important role in etiology of preterm delivery. Periodontal infection can serve as a reservoir of gram negative anaerobic organisms and their products, and proinflammatory mediators which could target the placental membranes via systemic circulation thus leading to preterm delivery or fetal growth restriction. The primary aim of this study is to examine the effect of maternal periodontitis on length of gestation and fetal growth. The secondary aim is to explore the association between periodontitis and serum levels of TNF-alpha. The proposed prospective nested case-control study will request pre-existing radiographs from Viva participants.

TITLE: **Treating PMS/PMDD: Research Versus Clinical Reality** **NIMH**
P.I.: **Kimberly Yonkers, M.D.**
INSTITUTION: **Yale University School of Medicine, New Haven, CT**
GRANT NO.: **1R21MH62379-01A1**
KEYWORDS: **women's health, menstrual cycle, mood disorders, mental health**
TYPE STUDY: **Clinical**
AMOUNT: **$100,000**

Moderate to severe premenstrual disturbances afflict up to 15-20% of women. After years of treatment research that was notable for inconsistent findings, researchers have identified agents that effectively treat women suffering from these conditions. An appealing treatment modality for ameliorating symptoms in women with premenstrual dysphoric disorder (PMDD) is the use of SRIs only during the luteal phase of the menstrual cycle, an approach supported by several randomized clinical trials. Medication administered by this way limits both drug exposure and side effects to the symptomatic phase of the cycle and is often preferred by patients. Given positive efficacy studies for luteal-phase dosing, it is likely that the Food and Drug Administration will approve the use of this modality for the treatment of moderate to severe premenstrual conditions such as PMDD. Yet, this is a treatment modality that has only been evaluated in controlled clinical trials, and features that may have enhanced positive study results (monitoring ovulation, compliance counseling by vigilant study staff, and direction regarding when to initiate medication) are noticeably absent in routine clinical practice. Furthermore, evidence suggests that patients in clinical trials who were able to comply with luteal-phase dosing are not representative of women commonly seen in clinical practice, and thus the feasibility of luteal-phase dosing is unclear. The specific aims of this application are to: 1) Evaluate whether women in a primary care ob-gyn practice with moderate to severe PMS will be willing and able to adhere to psychotropic medication treatment that is limited to the luteal phase of the menstrual cycle; 2) Determine whether specific patient characteristics (suffering from moderate to severe PMS that does not meet criteria for PMDD versus suffering PMDD; having another co-occurring psychiatric or general medical condition that is not limited to the luteal phase of the cycle versus not having other disorders) influence response to intermittent SRI treatment; 3) Evaluate whether a retrospective scale administered in conjunction with a psychiatric screening scale can identify women with moderate to severe premenstrual changes; 4) Compare and select outcome measures that are most able to show improvement in premenstrual symptoms after treatment with an SRI; and 5) Collect symptom data on treatment as usual in order to estimate the effect size required for a subsequent study.

VIOLENCE

TITLE: **NAS Panel on Risk and Prevalence of Elder Abuse and Neglect** **NIA**
KEYWORDS: **aging, violence, behavior**
AMOUNT: **$75,000**

The purpose of this initiative is to request NAS/NRC to organize a Panel on Risk and Prevalence of Elder Abuse and Neglect. The panel meetings will integrate expert knowledge in the field and provide advice on developing the methodology and design for a national probability sample on abuse and neglect. It will also suggest instrumentation for measuring highly sensitive and stigmatized behaviors and provide cross-fertilization for studies of child abuse, HIV, violence against women, and criminal behavior. NAS/NRC's Committee on National Statistics (CNSTAT) will be asked to provide expertise in the design of surveys to measure low prevalence phenomena in such populations as older, institutionalized women. A panel will help develop options for the research design, specify appropriate populations for sample inclusion (e.g., men, women, the institutionalized, racial/ethnic categories), and design instrumentation that can be used to detect incidents of elder abuse and neglect reliably and validly. The panel will evaluate the potential for pilot studies needed to develop instruments that can detect abusive behavior. The panel will also discuss issues related to confidentiality and data sharing. In addition, the panel will be asked to make recommendations regarding the scope of a national research effort on elder abuse and neglect which will include institutionalized victims of abuse and neglect and issues related to data collection on victims suffering from dementia.

TITLE: **Hispanic Battered Women's Experiences of Health Care** **NINR**
P.I.: **Ursula A., Kelly, MSN**
INSTITUTION: **Boston College, Chestnut Hill, MA**
GRANT NO.: **1F31NR07686-01**
KEYWORDS: **mental health, partner victimization, underserved populations, women's health**
TYPE STUDY: **Clinical**
AMOUNT: **$26,150**

The purpose of this descriptive exploratory qualitative study is to improve health care providers' understanding of the health care experiences of Hispanic battered women. The specific aim of the study is to identify aspects of health care interactions with primary care providers (PCPs) that Hispanic battered women perceived as helpful, supportive or positive, or that made a difference in the women's experience of living with the abuse. This research will provide patient-centered information that will lead to improved health care interventions for this population, increased patient satisfaction with health care, and enhanced patient-provider relationships. Domestic abuse is significant health problem which PCPs are well-positioned to address. There is a lack of understanding of this problem, and the needs of victims of abuse, from the patients' perspective, particularly Hispanic women. This study will use feminist methodology to elicit and articulate Hispanic battered women's experiences of health care, the meaning they give to those experiences, and the health care responses they find helpful. Data will be collected through interviews with Hispanic women who are survivors of domestic abuse, and will be analyzed via content analysis. The resulting description of the women's experiences will enhance PCPs understanding of effective health care interventions for Hispanic survivors of domestic abuse.

TITLE: **Biophysical and Immunologic Responses to Battering** **NINR**
P.I.: **Anne B. Woods, MPH**
INSTITUTION: **Johns Hopkins University, Baltimore, MD**
GRANT NO.: **1F31NR07600-01**
KEYWORDS: **intimate partner, neurosciences research, violence, women's health**
TYPE STUDY: **Clinical**
AMOUNT: **$26,150**

Intimate partner violence (IPV) has significant long-term effects on women's health. In spite of persistent findings of increased infections, assessment of immune system function among battered women is one of the weakest areas of current research; and mental and physical health effects are typically investigated as separate, distinct outcomes. Conceptualizing the response to abuse within a stress response framework that links mental health effects on HPA axis regulation with Th1/Th2 cell modulation may help to explain the impact of IPV on abused women's immune function. The major purposes of this predictive correlational study are to: (1) identify the prevalence of intimate partner violence among women who utilize health care services at a clinic for the uninsured in Baltimore, MD; (2) to identify the relationship of depressive, post-traumatic stress disorder, and comorbid depressive/PTSD symptoms with immune function; and (3) to identify predictors of immune system alterations among a sample of abused women. All women who present for care at the Shepherd's Clinic will complete a brief health questionnaire including the Abuse Assessment Screen. Eligible women who screen positive for IPV along with a comparable, non-abused control group, will be invited to

participate in an interview to collect quantitative data on partner abuse, depressive and PTSD symptoms, and health problems. Medical chart review will confirm past immune system disorders. Serum levels of Th1 (interferon-() and Th2 (interleukin-10) cytokines, which are mediated through cortisol, will assess modulation of immune system function. Descriptive statistics, Chi-square, ANOVA and ANCOVA techniques will be used to determine the relationship of mental health disorders and immune system function. Multiple logistic regression will investigate predictors of Th1/Th2 cell modulations. This proposed study will contribute information on the effects of intimate partner violence and mental health symptoms on immune function.