A Working Document

NIH Research And Other Efforts Related To The Menopausal Transition

(Updated March 2005)

The Office of Research on Women's Health

and the

Coordinating Committee on Research on Women's Health

National Institutes of Health

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FOREWORD

This represents the third compilation of National Institutes of Health funded research related to the menopausal transition, prepared by the Office of Research on Women's Health in the Office of the Director. It is intended as a resource to describe in brief the many aspects of the menopausal transition that are currently the subject of research by NIH supported investigators.

The report is prepared in collaboration with the women's health liaison from each NIH institute and center (IC) who are all members of the NIH Coordinating Committee on Research on Women's Health. The information received from each IC is incorporated as submitted.

It is not intended that this report be exhaustive in the information it provides, but rather to reflect the vast interest of investigators in the menopausal transition and the extensive support of the NIH components of related research.

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Introduction

The median age of women at cessation of menstrual bleeding is 50 to 51 years. With an average life expectancy of 79.7 years, most women can expect to spend one-third to one-half of their lives post-menopause. In the United States alone, there are an estimated 42.19 million women over age 50 including 39.9 million postmenopausal women and 1.55 million women (4,255 per day) who reached menopause[1]. Additionally, a woman who reaches age 54 can expect to reach the age of 84 years with more than two-thirds of the US population reaching 85 years or longer[a]. By the year 2020, the number of US women over age 55 is expected to be 45.9 million.

In 1998, there were more than 477 million postmenopausal women in the world, with approximately 9% expected to live to age 80. By 2025, the number of postmenopausal women is expected to rise to 1.1 billion. A women's lifespan is expected to rise to 72 years worldwide by 2025 (82 in more developed countries).

According to a 1998 study, one in three women between ages 45 and 64 were on hormone therapy[2] (HT), and there were about 17.5 million women total taking HT to combat the biological effects of menopause[3]. Understanding the biology, symptomology, and socio-cultural implications of the menopausal transition is essential in addressing the health concerns of the aging female population. Therefore, the Office of Research on Women's Health (ORWH) is collaborating with NIH Institutes and Centers (IC) to develop a comprehensive report on NIH supported research and programs on the menopausal transition.

Initial information for this report was obtained through queries of the NIH Computer Retrieval of Information on Scientific Projects database (CRISP) and the National Library of Medicine website,

[1] North American Menopause Society, http://www.menopause.org/aboutmeno/sga.pdf
[2] "Health Concerns Across A Woman's Lifespan: The Commonwealth Fund 1998 Survey Of Women's Health." Collins, K.S., Schoen, C., Joseph, S., Duchon, L., Simantov, E., Yellowitz, M. May 1999.
[3] "Study: Hormones Don't Protect Women From Heart Disease." Okie, S.Washington Post. July 24, 2001.

www.ClinicalTrials.gov. Results of these queries were forwarded to the appropriate IC for verification, or revision. This report summarizes the basic science and clinical research, recent research results, and pending research studies on the menopausal transition currently funded by each Institute and Center, as provided through the Coordinating Committee on Research on Women's Health (CCRWH) representative from each NIH component.

Beginning with the definition of menopause as stated in the "World Health Report 1998," published by the World Health Organization (WHO), this report provides a summary, by IC, of menopause related research currently being funded by the NIH. Five IC's reported no current research on menopause: National Human Genome Research Institute (NHGRI), Fogarty International Center (FIC), National Institute of Biomedical Imaging and Bioengineering (NIBIB), Center for Scientific Review (CSR) and the National Library of Medicine (NLM).

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OPLA	Anne Houser	
OITE	Pat Sokolove	

Working Definitions of Menopause

From the World Health Report, 1998
World Health Organization, Geneva, Switzerland

TERM	SOURCE
Menopause (natural menopause) The term natural menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhoea, for which there is no other obvious pathological or physiological cause. Menopause occurs with the final menstrual period (FMP), which is known with certainty only in retrospect a year or more after the event. An adequate biological marker for the event does not exist.	WHO*
Perimenopause The term perimenopause should include the period immediately prior to the menopause (when the endocrinological, biological, and clinical features of approaching menopause commence) and the first year after menopause.	WHO
Menopausal transition The term menopausal transition should be reserved for that period of time before the FMP when variability in the menstrual cycle is usually increased.	WHO
Climacteric This phase in the aging of women marks the transition from the reproductive phase to the non-reproductive state. This phase incorporates the perimenopause by extending for a longer variable period before and after the perimenopause.	IMS**
Climacteric syndrome The climacteric is sometimes, but not necessarily always, associated with symptomatology. When this occurs, it may be termed the "climacteric syndrome."	IMS
Premenopause The term premenopause is often used ambiguously to refer to the one or two years immediately before the menopause or to refer to the whole of the reproductive period prior to the menopause. The group recommended that the term be used consistently in the latter sense to encompass the entire reproductive period up to the FMP.	WHO

Postmenopause WHO

The term postmenopause is defined as dating from the FMP, regardless of whether the menopause was induced or spontaneous.

Premature menopause WHO

Ideally, premature menopause should be defined as menopause that occurs at an age more than two standard deviations below the mean estimated for the reference population. In practice, in the absence of reliable estimates of the distribution of age at natural menopause in populations in developing countries, the age of 40 years is frequently used as an arbitrary cut-off point, below which menopause is said to be premature.

Induced menopause WHO

The term, induced menopause, is defined as the cessation of menstruation, which follows either surgical removal of both ovaries (with or without hysterectomy) or iatrogenic ablation of ovarian function (e.g. by radiation or chemotherapy).

**WHO – World Health Organization*
***IMS – International Menopause Society*

Web Resources on Menopausal Hormone Therapy

National Institutes of Health
http://www.nih.gov/PHTindex.htm

National Heart, Lung & Blood Institute
http://www.nhlbi.nih.gov/health/women/index.htm

National Cancer Institute
http://www.cancer.gov/newscenter/estrogenplus

Medline Plus
http://www.nlm.nih.gov/medlineplus/hormonereplacementtherapy.html

National Center for Complementary and Alternative Medicine
http://nccam.nih.gov/health/alerts/menopause

Office of Research on Women's Health

> **Menopause Management and Hormone Therapy**
> http://www4.od.nih.gov/orwh/menopause.html

National Institute on Aging
http://www.nia.nih.gov/health/pubs/menopause

MENOPAUSE RELATED RESEARCH

By Institute or Center

National Cancer Institute

(NCI)

National Cancer Institute

Description:

The National Cancer Institute (NCI) supports a broad range of research related to the menopausal transition and cancers in women. A spreadsheet is provided describing relevant research grants which have been funded recently or are currently being funded by NCI.

Search Words: *menopause; perimenopause; postmenopause; hormone therapy; hormone replacement therapy (HRT); estrogen replacement therapy (ERT)*

The NCI provides a digest page on Menopausal Hormone Use, http://www.cancer.gov/clinicaltrials/digest-postmenopausal-hormone-use on the NCI website. The page provides a fact sheet with questions and answers on menopausal hormone use, links to important information throughout the National Institutes of Health, updates on recent research results, and links to information on current clinical trials.

The NCI also provides information on early menopause that may occur due in women who have their ovaries removed before natural menopause.
http://ovariancancer.gog199.cancer.gov/premature.html

NCI Menopause Related Grants (submitted March 2005)

(Includes projects funded and coded through December 2004, but may not include all projects funded in Fiscal Year 2004)
To search NCI grants, go to http://researchportfolio.cancer.gov/

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
CA17054	Ross, Ronald	2005	University of Southern California	Iatrogenic Causes of Cancer	Breast Etiology/Exogenous Factors in the origin and cause of cancer; Interactions of Genes and/or Genetic Polymorphisms with Exogenous and/or Endogenous Factors	This project is a subproject of an ongoing program project grant.: Combination estrogen-progestogen therapy for postmenopausal women has become increasingly popular since the mid-1970s. Early on, clinicians widely believed that, in addition to reducing the risk of endometrial cancer associated with unopposed estrogen therapy, such therapy would reduce the risk of breast cancer. It was assumed that progestogens had an "anti-estrogen" effect on breast tissue comparable to that on the endometrium, with the results of a large prospective study of women receiving various modes of therapy widely quoted as supporting this view. However, the finding of an increased risk of breast cancer associated with combination oral contraceptive therapy given around the time of menopause and the observation that breast tissue mitotic activity peaks during the luteal phase of the menstrual cycle suggest estrogen-progestogen therapy may actually increase breast cancer risk in postmenopausal women. Experimental data support this notion, as does suggestive but inadequate data on use of progestogen-only contraceptives. One prospective epidemiologic study of combination therapy and breast cancer also suggests an increased risk but the number of cases was small. To determine the effect on breast cancer risk of combination estrogen-progestogen hormonal replacement therapy as well as of unopposed estrogen replacement therapy, we have been conducting a large case-control study. Preliminary analysis from 1355 cases and 884 controls indicate that unopposed estrogen therapy moderately increases breast cancer risk overall, but in a duration and dose-related fashion. The addition of a progestogen appears to enhance these estrogen-related effects and leads to a further increase in breast cancer risk. We wish to expand this study to address more adequately duration and latency effects, the possible interaction between use of hormone replacement therapy and other breast cancer risk factors, and to confidently assess differences in risk levels with use of combination versus unopposed replacement therapy. Breast cancer patients are English- or Spanish-speaking women aged 55 and over, of all races except Asian, born in 1923 or later, and identified by our population-based tumor registry over a six year period. Controls are individually matched to cases by age (+3 years), race and neighborhood of residence. A structured interview form supplemented by a comprehensive manual containing color photographs of all types of estrogen and progestogen pills is employed for the in-person interviews. Validation of hormone therapy is accomplished by a review of physician records. The 3000 case-control pairs to be interviewed will allow for the evaluation of the effects of estrogen and estrogen- progestogen therapy on breast cancer risk in the presence of possible confounding variables, such as age at and type of menopause and weight, and for testing for interactions between hormone therapy and other breast cancer risk factors, such as benign breast disease, and for careful evaluation of the effects of duration and latency.
CA18119	Katzenellenbogen, Benita	2009	University of Illinois Urbana-Champaign	Antiestrogens--Mechanism of Antagonist Action	Breast Cancer-Related Biology	DESCRIPTION (provided by applicant): Antiestrogens and SERMs (selective estrogen receptor modulators) such as tamoxifen and raloxifene are the most widely used agents in the treatment of hormone-responsive breast cancer and have proved to be very effective in breast cancer prevention. They are likely to play increasingly important roles in menopausal hormone replacement therapy as well. While it has long been known that the estrogen receptor (ER) is required for the actions of estrogens and SERMs, it is increasingly appreciated that the activity of the ER and the tissue selectivity of SERMs are markedly influenced by coregulator proteins. Also, the action of ER influences the expression pattern of a remarkable number of genes through a diversity of modes. In this project, we will combine modern technologies in an innovative two-pronged approach to understanding the molecular basis of SERM action: (a) a targeted investigation of the role of an ER-specific coregulator, REA (repressor of estrogen receptor activity), through the development of an REA knockout mouse, together with comparative studies on the influence of other corepressors in the action of SERMs, and (b) a global analysis of gene regulation by SERMs using microarrays, together with complementary bioinformatic, molecular, and biochemical analyses of regulated function. This research should provide a clearer understanding of the gene networks through which SERMs act, the cellular factors that determine SERM effectiveness and tissue selectivity, and the gene-regulating activities that contribute to their beneficial anti-proliferative and tumor suppressive actions in breast cancer treatment and prevention, and provide the optimal balance of tissue selective activities for hormone replacement therapy.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
CA34588	Toniolo, Paolo	2002	New York University	New York University Women's Health Study	Breast Endogenous Factors in the Origin and Cause of Cancer	With this competing renewal, we seek to expand the initial observations of the NYU Women's Health Study showing a strong association between endogenous estrogens (estrone and estradiol) and post-menopausal breast cancer. Of particular interest are subjects who were sampled between 5 and 12 years prior to breast cancer diagnosis. We propose to expand the cohort by 3.5 additional years to identify all subjects developing breast chancer as of the end of 1997. With this additional effort, the cohort will be have been followed for an average of 12 years. We expect to identify a total of 1,548 incident cases of malignant tumors, including approximately 603 cases of invasive breast cancer (257 pre- and 346- menopausal). Of those 124 pre- and 185 post-menopausal cases will have been diagnosed 5 years or more after blood donation. The major aim of the proposal is to examine the association between blood levels of endogenous estrogens (estrone, estrone sulfate, estradiol, bioavailable estradiol), sex-hormone-binding globulin (SHBG) and breast cancer risk among subjects who samples were obtained between 0.5 and 12 years before the date of index diagnosis. We are especially eager to determine whether these associations hold when time to diagnosis increases, i.e., whether the associations are present in the early stages, or even before, disease initiation. We are interested also in determining whether the major androgenic precursors of estrongens (androstenedione and testosterone) are associate with breast cancer risk in the same population. Breast cancer cases and individually matched controls form the cohort will be included in the nested case-control study and their serum samples will be retrieved from storage and analyzed for levels of endogenous hormones utilizing state-of-the-art biochemical methods. Subjects who were pre-or post-menopausal at the time of cohort enrollment (i.e., at the time of the collection of baseline samples) will be considered in separate statistical analyses.
CA40104	Haslam, Sandra	2008	Michigan State University	Stroma and Mammary Gland Cell Proliferation	Breast Cancer-related Biology	DESCRIPTION (provided by applicant): Progestins (P) are major mitogens in the adult human breast and contribute significantly to breast cancer risk. Since P are widely used in oral contraceptives and in postmenopausal hormone replacement therapy it is critically important that their mechanims of action be understood. It is the goal of the proposed research to delineate the mechanisms of P-dependent proliferation in the normal mammary gland. In the current grant period, using the mouse mammary gland model, we have developed a minimally-supplemented, serum-free collagen gel primary culture system in which mammary epithelial organoids, made up from both luminal epithelial and myoepithelial cells, proliferate and undergo alveolar morphogenesis in response to P. In addition to P, these responses require mammary stroma derived-hepatocyte growth factor (HGF). Treatment with HGF alone induces proliferation and tubulo-ductal morphogenesis, whereas P alone does not induce proliferation but induces lumen formation that is associated with increased apoptosis. HGF+P increase proliferation above HGF alone and cause a change from ductal to alveolar morphology. This is a novel in vitro demonstration of a mitogenic and morphological response to P that recapitulates the proliferative and alveologenesis response to P in vivo. In addition a pro-apoptotic response to P in normal mammary cells has been identified. In this proposal we will determine whether and how P acts in the cytoplasm, possibly through an SH3 binding domain on the progesterone receptor (PR), to affect HGF/Met-activated pathways associated with mammary-specific tublogenesis (FAK, SHIP-1, PI3-K) and proliferation (ERK, Src/Myc) to inhibit tubulogenesis, promote proliferation and cause alveologenesis. We will also determine the effect of PR action in the nucleus, via its transcriptional activation function, on the expression of P-responsive target genes relevant to alveologenesis (Wnt-4) and proliferation (Met, cyclin D1, Myc). In addition will also identify the specific cells types (luminal epithelial, myoepithelial cells) in which these effects of P occur. Using cultures derived from PRA null or PRB null mice we will also determine the role of the two PR isoforms (A and B) in proliferation and alveologenesis. The long-term goal of this proposal is the delineation of the mechanisms of P-dependent growth regulation in the adult normal mammary gland that may lead to novel strategies for the prevention and treatment of breast cancer.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
CA46475	Colditz, Graham	2004	Brigham and Women's Hospital	Benign Breast Disease and Risk of Breast Cancer	Breast Endogenous & Exogenous Factors in the origin and cause of cancer	DESCRIPTION: (Adapted from the Investigator's Abstract) The prevalence of benign breast disease and the substantial risk of breast cancer experienced by women with atypical hyperplasia makes our efforts to understand the biology of this relationship a high priority. We hypothesize that the relation between duration of use of postmenopausal hormones and risk of breast cancer is stronger among women with than without atypical hyperplasia; the expression of estrogen receptor activity is higher among women with atypia than among those with non-proliferative disease; retinoid-x receptor is expressed by a higher proportion of women with proliferative benign lesions. This new component of the study using blocks from the cases and controls to assess expression of receptors will further our understanding of the biologic mechanisms for the progression of benign lesions to breast cancer. Centralized histopathology reviews by expert breast histopathologists apply standard criteria. The extension of case accrual through the year 2000 will add 218 cases of breast cancer and 873 controls. This will give a final data set containing over 600 cases and 2500 controls. Overall, blocks will be available from 358 cases and using 2 controls per case (716 controls) to evaluate receptor status. Drs. Graham Colditz, Stuart Schnitt, and James Connolly have collaborated over the past decade to build this large histopathology resource and to evaluate categories of benign change in relation to risk of subsequent breast cancer. The Nurses' Health Study research group provides a rich resource of investigators to critically appraise the proposed research as it moves forward. This study is a key component of the Risk Identification and Risk Reduction Program within the Harvard Comprehensive Cancer Center/Dana Farber Cancer Institute.
CA49449	Hankinson, Susan	2009	Brigham and Women’s Hospital	Biochemical Markers in the Nurses’ Health Study Cohort	Breast Colon and Rectal Gastrointestinal Endogenous & Exogenous Factors in the origin and cause of cancer	DESCRIPTION (provided by applicant): In this competing renewal, we propose to build upon and extend our recent work on endogenous hormones and risk of breast cancer and also to evaluate several new breast cancer hypotheses. In addition, we propose to address a number of new hypotheses in relation to risk of ovarian cancer, a highly lethal cancer in women for which few prospective evaluations of biomarkers have been conducted. To accomplish these aims, we will conduct two nested case-control studies using already collected biologic samples from the Nurses' Health Study (for breast and ovarian cancers), and both the Women's Health Study and Nurses' Health Study II (for ovarian cancer only). Specifically, we will evaluate plasma estrogen metabolites, prolactin (using two blood samples collected 10 years apart), urinary melatonin, and urinary vs. plasma estrone sulfate, all in relation to breast cancer risk. Further, we will evaluate the independent contribution of endogenous sex steroids to the Gall and Rosner individual breast cancer risk prediction models. We also will evaluate plasma insulin like growth factors, androgens, vitamin D, and polymorphisms in both the progesterone receptor and vitamin D receptor in relation to ovarian cancer risk. Our proposed ovarian cancer aims, with 282 cases in plasma analyses and 521 cases in genetic analyses (all with 2 controls per case), will provide either the first or by far the most detailed prospective assessment of these potentially important risk factors. Finally, as a methodologic aim, we propose several pilot studies to evaluate the feasibility of using mass spectrometry technology (SELDI-TOF) in our cohorts to identify plasma protein profiles that predict subsequent cancer risk. Overall, the large size of these cohorts, their prospective design, high follow-up rates, detailed exposure data collected over many years, and the availability of archived plasma, DNA and urine specimens provides a unique opportunity to test a number of hypotheses of public health importance.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
CA58420	Rosenberg, Lynn	2009	Boston University	Follow-up Study for Causes of Illness in Black Women	Breast Endometrial Female Genital System Endogenous & Exogenous Factors in the origin and cause of cancer	DESCRIPTION (provided by applicant): We propose to continue the largest follow-up study of the health of African-American women yet undertaken, the Black Women's Health Study (BWHS). The overall aim is to assess potential risk and preventive factors for breast cancer, other cancers and important nonmalignant conditions. The purpose of the present grant proposal is to support continued data collection, and analyses that focus on breast cancer. The BWHS cohort was established in 1995 when African-American women aged 21-69 years from across the U.S. completed mail questionnaires, providing data on demographic factors, medical and reproductive history, body size, use of oral contraceptives and other drugs, physical activity, smoking, diet, and other factors. 59,000 women have been followed every two years by mail questionnaires that obtain information on exposures and incident disease, with follow-up rates in each cycle exceeding 80% of the original cohort. Methods for managing the data and validating exposures and outcomes have been established. After follow-up in the proposed grant, 1,400 cases of incident breast cancer will be available for analysis. We will prospectively assess the relation of aspects of body mass index, weight gain, body fat distribution, physical activity, diet, oral contraceptive use, cigarette smoking and hair relaxer use to breast cancer incidence with sufficient power to assess effects in important subgroups, e.g. strata of menopausal status and body mass index. We will also assess the adequacy of the Gall model for predicting breast cancer risk; the model, used to assess the eligibility of women for prevention trials, has never been tested in black women. Although there have been numerous studies of some of these issues in white women, differences in risk factors might modify associations in black women. Importantly, this proposal is not simply a repeat of studies done in white women. It addresses many issues particularly relevant to black women on which data are lacking, such as the influence on breast cancer incidence of high levels of obesity or weight gain, or of physical activity within levels of obesity. The results will fill large gaps in knowledge about risk factors for breast cancer incidence. In addition, the proposed data collection together with DNA being collected under another grant will provide a unique resource for assessing genetic hypotheses concerning cancer and other illnesses in black women.
CA60050	Shapiro, Charles	1999	Ohio State University	Premature Ovarian Failure in Breast Cancer Patients	Bone, Osteosarcoma/Malignant Fibrous Histiocytoma, Breast Patient Care and Survivorship Issues	Adjuvant chemotherapy reduces mortality rates in women with breast cancer. Because many breast cancer patients have prolonged survival after adjuvant treatment the long term health effects associated with adjuvant chemotherapy are important to evaluate. Premature ovarian failure (menopause) occurs in approximately 70% of premenopausal breast cancer patients who receive adjuvant chemotherapy. The resulting estrogen deficiency and premature menopause in women with breast cancer may result in accelerated loss of bone, and the risk for subsequent skeletal fractures (osteoporosis). To investigate whether breast cancer patients who develop chemotherapy-induced premature ovarian failure experience accelerated bone loss, in Specific Aim #1 we will prospectively examine bone mineral density and biochemical indices of skeletal homeostasis in premenopausal breast cancer patients who develop chemotherapy-induced premature ovarian failure. In Specific Aim #2 we will test whether nasal spray calcitonin, an inhibitor of bone resorption, prevents bone loss in these women. Premenopausal breast cancer patients with 0-3 axillary nodal metastases will be recruited to participate in this research study. One-hundred such women will undergo baseline evaluations of menstrual status, follicle-stimulating hormone (FSH), estradiol (E2), and progesterone, (P), reproductive history questionnaire, activity questionnaire, self-rating depression questionnaire, 3-day dietary evaluation, quantitative measurements of bone mineral density of the lumbar spine and proximal femur, and biochemical indices of skeletal homeostasis (serum ionized calcium, parathyroid hormone, and osteocalcin). (DEXA) method. Following the baseline evaluation adjuvant chemotherapy will be administered. The baseline measurements will then be repeated at 6, 12, and 24 months. At the 12 month evaluation women with chemotherapy-induced ovarian failure (approximately 70% of participants) will be randomly allocated to either one year of nasal spray calcitonin (200 IU/day) plus 1500 mg of oral daily calcium intake or nasal spray placebo plus 1500 mg of oral daily calcium intake in a double-blind placebo-controlled trial. Tamoxifen may also prevent bone loss and inhibit bone resorption. In Specific Aim #3 we will test whether tamoxifen prevents bone loss in breast cancer patients with chemotherapy-induced ovarian failure. In this observational study 42 premenopausal breast cancer patients with 0-3 axillary nodal metastases who receive adjuvant chemotherapy and tamoxifen will undergo the baseline evaluation and study evaluations at 6, 12, and 24 months. These prospective studies in premenopausal women with breast cancer will provide insights into the natural history of hemotherapy- induced ovarian failure and bone loss, and the effects of nasal spray calcitonin and tamoxifen in preventing the accelerated bone loss in these women.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
CA63731	Buist, Diana	2005	Center for Health Studies	Breast Cancer Surveillance in a Defined Population	Breast Resources and Infrastructure Related to Cancer Control, Survivorship, and Outcomes Research Surveillance	DESCRIPTION: (Applicant's Description) This proposed project takes advantage of comprehensive surveillance data on more than 100,000 women offered breast cancer screening through a program with mailed reminders to schedule mammography examinations within a managed care plan (Group Health Cooperative of Puget Sound, GHC). Cancer outcome (mortality, late-stage disease) for the target population are collected through a Surveillance, Epidemiology, and End Results reporting (SEER) registry and are linked to health care process data (service use, mammography assessments). This proposal includes 3 specific aims: 1) To continue breast cancer data system development at GHC to; a) improve data system software, enhance data storage capabilities, and facilitate data retrieval; b) incorporate new data components pertinent to research, such as a targeted survey; and c) maintain and improve data quality assurance, report generation, and data file development; 2) To use the data system to conduct 5 initiatives: a) The effect of short-term hormone replacement therapy (HRT) cessation on mammographic density; b) The likelihood of additional imaging (mammography and ultrasound) and the associated costs among women stopping HRT compared to women continuing or never using HRT; C) The factors that explain the reduced sensitivity of mammography among younger women; d) The biologic and other factors that influence the likelihood of late-stage disease; and, e) The effect of screening interval on stage at-diagnosis; and 3) To conduct 5 research projects related to screening mammography: a) The additional effect of mammographic breast density on the 5-year risk of breast cancer; b) Screening sensitivity and specificity by phase of menstrual cycle; c) The association between mammographic findings and cancer among women with "probably benign findings"; d) The effect of computer assisted reading on mammography interpretive performance; and e) Biomarkers associated with nodal metastases at-diagnosis among screened women. By continuing our multi disciplinary collaboration and using carefully designed prospective observational and evaluative studies the investigators will contribute to improvements in breast cancer screening, and the understanding of breast cancer biology.
CA66189	Zeleniuch-Jacquotte, Anne	2000	New York University School of Medicine	Endogenous Estrogens and Endometrial Cancer	Endometrial Female Genital System Etiology/Exogenous Factors in the origin and cause of cancer	This study will investigate the relation between postmenopausal endogenous levels of estrogens and subsequent development of endometrial cancer. In premenopausal women, estrogens unopposed by progesterone are known to stimulate endometrial cell division, providing a rationale for the role of estrogens in endometrial carcinogenesis. In postmenopausal women, estrogen replacement therapy is associated with an increased risk of endometrial cancer. However, there is no direct epidemiologic evidence that the physiologically low levels of endogenous estrogens observed after menopause are positively associated with endometrial cancer risk. In the face of increasing long-term use of estrogen replacement therapy, to prevent cardiovascular disease and osteoporosis, a better understanding of the role of endogenous estrogens may help develop prescription guidelines. The proposed study will use an existing resource of frozen serum samples collected between 1985 and 1991 in a cohort of 6071 postmenopausal women enrolled in a study of breast cancer and endogenous hormones (New York University Women's Health Study, NYUWHS). The specific aims of the proposal are: 1) to identify incident cases of endometrial cancer, using follow-up information generated by the NYUWHS until mid-1998; 2) to conduct a case-control study of endometrial cancer nested within this cohort. Sixty incident cases of endometrial cancer are expected to occur by the end of follow-up. For each case, four controls, matched on age and date of blood donation, will be selected. Controls will have to be alive, free of disease and with an intact uterus at time of diagnosis of the case. Information on known risk factors will be collected through telephone interviews. Serum samples will be assayed for estrone, estradiol, percent estradiol bound to sex hormone binding globulin and percent free estradiol. Conditional logistic regression for matched data will be used to assess whether higher levels of endogenous estrogens are associated with a higher risk of endometrial cancer. The study will also investigate whether the role of obesity in endometrial cancer can be explained by its action on endogenous estrogens.
CA69334	McTiernan, Anne	2003	Fred Hutchinson Cancer Research Center	Exercise Effect on Sex Hormones in Postmenopausal Women	Breast Interactions of Genes and/or Genetic Polymorphisms with Exogenous and/or Endogenous Factors Interventions to Prevent Cancer: Personal Behaviors that Affect Cancer Risk	DESCRIPTION: (Adapted from Applicant's Abstract). The primary prevention of breast cancer is an important public health goal in this country. Exercise has been associated with a decreased risk for breast cancer. One mechanism may be via a hormonal pathway. Exercise decreases body fat, especially abdominal fat, which may be the mechanism through which exercise could lower concentrations of endogenous estrogens in premenopausal women. This application is a randomized interventional study that will test the effect of a one-year, moderate intensity exercise program on androgenous sex hormone profile in postmenopausal woman. Women (N=168) who are age 55-75 years will be randomized to either a one-year, moderate intensity exercise program or a controlled program of no change in exercise habits. Dietary intake will be assessed at baseline and follow-up through four-day food records. Serum hormones will be assayed at baseline and at end-of-study. These hormones include: total estrone, total estradiol, free estradiol, percent bioavailable estradiol, estrone sulfate, sex hormone binding globulin, albumin, testosterone, free testosterone, androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulfate, insulin, glucose and triglycerides. The ratio of urinary 2-hydroxyestrone (2-OHE1) to 16a-hydroxyestrone (16-alpha-E1), an estrogen metabolite ratio which may be associated with breast cancer, will also be assayed at baseline and at end-of-study. The effect of exercise on weight, body mass index, total fat mass, and body fat distribution will also be assessed. This study plans to give insight into possible mechanisms through which exercise may be associated with decreased risk of breast cancer.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
CA72099	Siegler, Ilene	2002	Duke University	Improving Cancer Risk Communication	Bladder, Breast , Lung, Respiratory System, Urinary System Behavior Related to Cancer Control Education and Communication	Major problems in cancer control are related, in part, to perceptions about cancer risk. These cancer control problems include smoking among African Americans and lack of adherence to mammography. In addition, risk perceptions affect women's decisions about whether to get mammograms and take estrogen replacement therapy (ERT). We propose to focus an outstanding group of Duke University investigators and a larger group of superb consultants on the vital topic of cancer risk communication. Never before has there been a concerted, comprehensive approach to cancer risk communication. Our goals are to develop a theoretical understanding of how people process risk information, develop and test population- sensitive measures of risk perception, develop useful techniques to improve risk comprehension and develop effective and cost-effective interventions to improve both decision making and cancer-related behaviors. As a result, we hypothesize that smoking will be reduced among African Americans and mammography use increased among women in their 50's and 60's. Moreover, we will improve decision making for mammography and ERT use. This CPRU includes three projects (one in which we will use biomarkers of genetic susceptibility to facilitate smoking cessation among African Americans, a study to facilitate informed decision making about ERT and a similar project on mammography), one developmental project (to develop an improved model of breast cancer risk prediction) and four cores (administration, biostatistics, cost-effectiveness and a risk laboratory), all developed with intentional synergy. All intervention projects include tailored print interventions and two will test the additional impact of telephone counseling, as well. All intervention-related data will be collected through telephone interviews. The use of core variables will permit comparisons across topics and populations. There will be sufficient African Americans and women to examine the effect of race and gender in these studies. We believe that this focused effort could lead to major advances in cancer control by developing the next generation of state-of-the-science interventions which will be grounded firmly in an understanding of cancer risk communication.
CA72787	Daling, Janet	2001	Fred Hutchinson Cancer Research Center	Calcium Channel Blockers in Breast Cancer Etiology	Breast Cancer Exogenous Factors in the origins and causes of cancer	DESCRIPTION: (Adapted from Applicant's Abstract). Although over one-third of all breast cancers are diagnosed among women aged 65-79 years, little epidemiologic research has specifically focussed on breast cancer in women of this age. Women of this age also commonly suffer from hypertension or coronary disease, and calcium channel blockers (CCBs) are often used to treat either of these conditions. Two recent studies, yet to be published, of women aged 65 and older, suggest that women who use CCBs may be at an increased risk of breast cancer. This suspected association is given biological plausibility by the observation that pharmacological blockade of the calcium channels can inhibit apoptosis (programmed cell death), the process whereby organisms eliminate unwanted cells (e.g., preneoplastic, initiated, damaged, excessive). In this sense, CCBs may be cancer promoters. The application proposes a case-control study of 1,000 women, aged 65-79, who reside in King County, Washington, who are on the Health Care Financing Administration (HCFA) tapes, and who are diagnosed with their first invasive breast cancer during the time period of January 1, 1997 through December 31, 1999. The personal interview responses of these women about drug use and other known risk factors for breast cancer will be compared to a control group of 1,000 women without breast cancer who will be identified through the HCFA tapes. Based on the preliminary studies and the evidence from in vitro studies on cells, it is posited that the use of CCBs increases the risk of breast cancer in older women. The plan is to assess whether calcium antagonists used in the treatment of hypertension and cardiovascular diseases promote breast cancer in women aged 65-79 years, and whether any one type of calcium channel blocker is more related to breast cancer than the other types. Since no studies have assessed present or past use of combined estrogen-progestin therapy in a large group of women this age, and the concurrent use of hormone replacement therapy (HRT) by these women may affect the proposed estimates of risk associated with CCBs, data will also be collected and analyzed on other drugs (viz., cimetidine, anti-depressants, lipid lowering drugs) frequently used by women in this age group.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
CA73638	Bolton, Judy	2006	University of Illinois at Chicago	Biotransformation of Estrogen to Carcinogenic Quinoids	Breast, Endometrial, Female Genital System Endogenous Factors in the Origin and Cause of Cancer	There is a clear association between excessive exposure to estrogens and the development of cancer in several tissues including breast and endometrium. The risk factors for women developing these cancers are all associated with longer estrogen exposure; early menses, late menopause, and long term estrogen replacement therapy. The mechanism(s) of estrogen carcinogenesis is unknown. Estrogen metabolites can act as chemical carcinogens by binding to cellular proteins or DNA. The catechol metabolites of estrogens are oxidized to o-quinones which undergo redox cycling generating reactive oxygen species which can contribute to the carcinogenicity through oxidation of DNA. Our preliminary data also show that the o-quinones are converted to additional reactive alkylating agents, quinone methides. The focus of this proposal is the role of quinoid metabolites in estrogen carcinogenesis. The specific aims are: 1. Establish the role of quinoids in the carcinogenic and cytotoxic effects of estrogens. The carcinogenic potential catechol estrogens will be studied in C3H 10T1/2 cells and their ability to act as tumor promoters will be examined in JB6 cells. The cytotoxicity of estrogens and catechol metabolites will be investigated in human ovarian and breast cancer cell lines. Biochemical parameters which serve as indicators of redox vs. alkylation mechanisms will be determined. 2. Determine the importance of quinoid formation to the metabolism of estrogens. The contribution of the o-quinone/p-quinone methide pathway to the biodegradation of estrogens will be determined. The ability of P450 to oxidize estrogens and their metabolites to o-quinones will be studied. Unsaturated estrogens which are components of the estrogen replacement drug, Premarin, will be investigated to probe electronic and steric effects on the biotransformation of estrogens to quinoids. 3. Investigate the effects of quinoid structure on electrophilic and/or redox reactivity. The electrophilicity of quinoids will be determined by measuring their rates of reaction with deoxynucleosides and by examining the extent of DNA alkylation. Their redox ability will be assessed by measuring reduction potentials, monitoring changes in NADPH and GSH levels in microsomal incubations, measuring reactive oxygen species, and examining autoxidation rates of the catechols. These data will determine the role of quinoids in the carcinogenic effects of estrogens and provide a basis for the development of estrogen replacement drugs devoid of carcinogenic activity.
CA76017	Heiss, Gerardo	2002	University of North Carolina Chapel Hill	HRT and Changes in Mammographic Density	Breast Exogenous Factors in the origin and cause of cancer	DESCRIPTION: Breast parenchymal patterns are depicted on mammograms as variations in radiographic density, which correspond to the relative amounts of fatty tissue (c.f., epithelial and stromal tissues). Mammographic density is highest in women with the greatest proportion of epithelial, stromal and connective tissues. Compared to no density, high density (>50%) has been consistently associated with significantly elevated long-term breast cancer risk, independent of age, menopausal status, or other breast cancer risk factors. Recently, several small case series have suggested that postmenopausal HRT may increase density in some postmenopausal women, although selection biases and imprecise measurement of exposure and outcomes (density) detract from the validity of these results. Given the small but persistent association of HRT with increased risk of breast cancer, and the increasing prevalence of HRT use among postmenopausal women, assessing the magnitude and correlates of the effect of HRT on mammographic density may contribute to improved understanding of the aetiologic role of exogenous hormones and to public health breast cancer prevention efforts. The objectives are to: 1) reliably estimate the quantitative effect of HRT on mammographic density in postmenopausal women; and 2) determine whether HRT-related density changes differ by ethnicity, age, time since menopause, body mass, or other breast cancer risk factors. This research is ancillary to the WHI, a long-term, multi-center, randomized trial of HRT in postmenopausal women. WHI participants are assigned to HRT (estrogen only for hysterectomized women, or combined progestin-estrogen for women with a uterus) or placebo. Working with the WHI clinical centers, measurements will be made of the percentage of breast density on participants' mammograms taken at baseline, one-year and two-year follow-up intervals, and then compared for longitudinal density change among treatment groups. The sample is comprised of 1200 women with adequate numbers in four ethnic groups: European, African, Hispanic and Asian/Pacific Islander Americans.
CA76366	Newcomb, Polly	2002	Fred Hutchinson Cancer Research Center	Hormone Replacement Therapy and Large Bowel Cancer Risk	Colon and Rectal Cancer Gastrointestinal Tract Cancer-related Biology Interventions to Prevent Cancer: Personal Behaviors that Affect Cancer Risk	The benefits and risks of estrogen replacement therapy continue to confuse women and their physicians. Recent evidence suggests that estrogen replacement may be associated with reductions in large bowel cancer, a common disease among postmenopausal women. Further study of this potentially important association would provide more precise estimates of the magnitude of effect, identify salient patterns of use, and, importantly, supply insights into the biology of this tumor in women. A population-base case-control study is proposed to evaluate the association between postmenopausal hormones and the occurrence of colorectal cancer. This study will specifically assess use of estrogens with and without progestin, the duration and currency of hormone use, and inter-relationships with body mass. Additional aims of this study are to elucidate the mechanisms of this inverse association, specifically the relationship of HRT to hormone receptors and proliferation in the bowel, and to examine the modifying role of more common cancer susceptibility genes influencing the metabolism of estrogens. Over a three year period, interviews will be conducted with 1,100 women with newly diagnosed cancer of the colon or rectum selected from the population. In addition to the structured telephone interview, fixed diagnostic tissue will be obtained from 540 case in order to evaluate estrogen-receptor status and proliferation markers. Blood samples on a sample of 600 (most with diagnostic tissue) cases and 600 controls will be obtained for genetic studies of polymorphisms relevant to estrogen metabolism and function, specifically CYP17 and the estrogen receptor gene. The proposed study and its extensions should provide clear evidence for the degree to which HRT is protective against colorectal cancer and permit the determination of some of the relevant pathways for that protection.

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CA77290	Rohan, Thomas	2006	Yeshiva University	Fat Reduction, HRT Use, and Benign Breast Disease Risk	Breast Exogenous Factors in the Origin and Cause of Cancer Surveillance	This proposed study is to evaluate the feasibility of studying women participating in the Dietary Modification (DM) and the calcium/vitamin D supplementation (CaD) components of the WHI clinical trial (excluding those who are also in the HRT component) to test the hypothesis that adoption of a low-fat dietary pattern is associated with reduced risk of proliferative forms of benign breast disease. Additionally, it is proposed that CaD alone, and in combination with low-fat dietary pattern, will also be associated with reduced risk. Also, it is proposed to conduct a nested case-control analysis of risk factors for proliferative forms of benign breast disease using cases identified in the control arms of the DM and CaD components of the trial. The feasibility study will run for 15 months, including 1 month to generate clinic-specific lists of eligible patients and to train clinics in the study methods, 12 months to conduct the review, and 2 months for data analysis. If the proposed study is feasible, the application predicts that it has the potential to provide insight into the etiology of the putative pre- malignant forms of benign breast disease and might identify an avenue for its prevention.
CA77355	Helferich, William	2006	University of Illinois Urbana-Champaign	Dietary Isoflavone, Tamoxifen, and Tumor Growth	Breast Systemic Therapies – Discovery and Development	Risk of breast increases with age and the majority of breast cancers are estrogen (E)-responsive. Approximately 75% of women with breast cancer are over 50 years old. Therefore, most women with breast cancer are postmenopausal. If a woman has E-responsive breast cancer it is likely that she is receiving antiestrogen tamoxifen (TAM) therapy. Considerable research has focused on the use of hormone replacement therapy (HRT) by women with E-responsive breast cancer and most oncologists/physicians do not recommend HRT to these women. However, there has been a dramatic increase in soy and estrogenic isoflavone consumption by postmenopausal women with breast cancer as a natural and perceived "safe" alternative to HRT. This "self-medication" with dietary estrogenic isoflavones for relief of menopausal and TAM-associated menopause-like symptoms is often done without their physician's knowledge. The safety of the dietary estrogenic isoflavones for women with E-responsive breast cancer and the potential for these phytoestrogens to negate the effectiveness of TAM therapy is a potential risk that has not been adequately evaluated. Our preliminary results indicate that the dietary genistein, the predominate isoflavone present in soy and isoflavone-containing supplements, can negate/overwhelm the inhibitory effects of TAM on E-stimulated tumor growth in athymic mice. In our proposed experiments, we will determine the minimum dietary dosage of genistein that can negate/overwhelm the inhibitory effects of TAM. Additionally, 30-40% of women consuming isoflavones can produce equol by enteric metabolism in the large intestine. This estrogenic metabolite can add to the dietary estrogen load and potentially increase breast cancer $sk in women (equol-producers) that consume isoflavones. We have developed a cost-effective method to convert formononetin to equol for use in both in vitro and in vivo tumor growth studies. This will allow us, for the first time, the ability to evaluate the interaction of equol with genistein and determine if this adds sufficient estrogenic activity to negate/overwhelm the inhibitory effects of TAM on E-stimulated tumor growth. In summary, our studies will determine if dietary estrogenic isoflavones and metabolites at physiologically relevant dietary dosages can negate/overwhelm the inhibitory effects of TAM on E-stimulated breast cancer growth.
CA77398	Wright, William	2003	Public Health Institute	Breast and Other Cancer in the California Teachers Cohort	Breast Cancer Nutritional Science in Cancer Prevention	A cohort of 133,000 California school teachers has been established by a collaborative group of epidemiological investigators with the goals of evaluating unresolved issues related to breast cancer risk factors and studying other important issues related to women's health. The teachers were recruited with a detailed multiple choice, optically-scanned mail survey. Scanning of the questionnaires has been completed and data editing is ongoing. Planned follow-up includes routine linkage with the California Cancer Registry and California mortality files, annual re-contact of cohort members for follow-up, and biennial contact for collecting additional risk factor exposure data and information on other health outcomes. The Specific Aims for this project are to: 1) test a series of unresolved and emerging hypotheses related to breast cancer aetiology (specifically associations with the lactation, hormone replacement therapy, abortion/miscarriage, dietary phytoestrogens, fibre, micronutrient consumption, alcohol intake, physical exercise and activities, family history of breast and other cancers, and active and passive cigarette smoke exposure); 2) conduct calibration/validation studies of the food-frequency questionnaire and self-reported information on family history of breast and other cancers reported in the baseline questionnaire; and 3) follow this cohort for five additional years, during which time, two or more questionnaires will be mailed to update initial exposure assessments, collect new exposure information, and assess additional disease outcomes for testing novel hypotheses of major importance to women's health, in a timely manner. During the next five years, 2,025 invasive incident and 390 in situ incident breast cancers are anticipated which will provide ample statistical power to address each of the proposed hypotheses in detail. The California Teachers Study presents a rare opportunity to study women's health, because of the size of the cohort, the uniformly high level of education among teachers, their experience with survey instruments, their diversity of exposures and geographic residences, and the relative ease with which they can be followed in California. This research is intended to substantially increase knowledge of preventable risk factors for cancer and other health outcomes.

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CA77530	Lydon, John	2003	Baylor College of Medicine	Progesterone Receptor and Breast Cancer	Breast Cancer-related Biology	Breast cancer is recognized as the most prevalent malignancy among women in North America with a life time risk currently estimated to be one in eight. Most importantly, reproductive history or more specifically steroid hormonal status has been shown to be an important risk factor. Recently, I generated a progesterone receptor (PR) knockout (PRKO) mouse that has demonstrated that progesterone (P), and its receptor, the PR, are absolutely required for normal mammary gland proliferation and differentiation. The involvement of P in mammary tumorigenesis has been a matter of controversy for several years mainly because P can protentiate or inhibit mammary tumorigenesis. To clarify the complex temporal relationship between P and mammary tumorigenesis, the PRKO mouse will be utilized to determine whether the P indued-proliferative signal has a role to play in breast cancer by investigating the effects of removing PR function on mammary tumor progression. The specific aims of this proposal are to: 1) evaluate whether removal of PR function alters murine susceptibility to carcinogen-induced mammary tumorigenesis at the morphological, histological, and molecular level; 2) determine whether PR function has a role in the development of hormone dependent mammary tumors exhibited by the Grunder mouse and define whether the PR has an involvement in the progression of these tumors to a hormone independent phenotype; and 3) to define the distinct effects of mammary epithelial and stromal derived PR populations on mammary development and tumorigenesis by using reciprocal mammary gland transplantation technology. Apart from advancing our current understanding of P's contribution to mammary tumorigenesis, information from these studies will aid in the design of effective strategies for breast cancer prevention and treatment as well as prompting a reevaluation of the current use of progestins in contraception and postmenopausal hormonal replacement therapies.
CA77596	Strom, Brian	2003	University of Pennsylvania	Molecular Susceptibility to Hormone Induced Cancer	Breast, Etiology/Endogenous Factors in the origin and cause of cancer	There is strong evidence that a combination of inherited genotypes and hormone exposures influenced breast cancer risk. Furthermore, inherited genotypes involved in the metabolism of steroid hormones may also modify a woman's risk of developing breast cancer. Knowledge about interactions of these factors in breast cancer etiology may improve the ability to identify women at increased breast cancer risk. This knowledge may in turn be used to target women for breast cancer prevention or treatment strategies. We propose a population-based case-control study that will directly address the complex, multi-factorial etiology of breast cancer that involves the interaction of genotypes and hormonal risk factors. These hormonal factors include endogenous exposures measured by parity-related events, and exogenous exposures to compounds such as estrogen replacement therapy (ERT). This study will address a number of specific hypothesis. First, we will evaluate whether candidate susceptibility genotypes are associated with breast cancer in a case-control analysis. The genes of primary interest will be CYP1A1, CYP3A4, and glutathione-S-transferase mu and theta genes, which are involved in the metabolism of steroid hormones. Second, we will evaluate whether genotypes and other reproductive risk factors interact in breast cancer etiology, and whether knowledge of genotypes will improve our understanding of breast cancer etiology once hormonal risk factors (e.g., reproductive history or ERT) are known. Third, we will evaluate whether the genetic and hormonal etiology of breast cancer differs by race. In order to address these hypotheses, we will undertake a study in the Greater Delaware Valley using an existing network of hospitals to identify a population-based sample of cases and random digit dialed controls. The sample will consist of 1200 White and 1200 Black subjects. Risk-factor information will be obtained from a telephone interview, a biosample containing DNA will be collected using a non-invasive cheek swab method. and pathology information will be collected using standardized medical record abstraction. Analyses will be undertaken to evaluate the roll of candidate genotypes and hormonal risk factors in breast cancer etiology by race. These analyses will allow us to examine genotype by hormonal interactions in breast cancer etiology.

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CA77617	Session, Donna	2003	Mayo Clinic Rochester	Expression of Cyclin E in Gynecologic Malignancies	Female Genital System Ovarian Cancer Cancer-related Biology Endogenous factors in the origin and causes of cancer	The cyclins and their catalytic partners, cyclin-dependent kineses (Cdks) are key regulators of the cell cycle. Overexpression of cyclin genes has been described in several forms of human cancers. Preliminary evidence suggests that cyclin E is expressed in a subset of gynecological cancers, namely clear cell carcinoma of the ovary, endometrium and cervix. The first specific aim will focus on confirming the specificity of cyclin E for clear cell tumors of Mullerian origin. Expression of cyclin E will be assessed in different histological subtypes of epithelial ovarian, endometrial, cervical and renal cancers. Cyclin E specificity for gynecologic clear cell carcinomas may provide a useful diagnostic marker to help distinguish a pelvic tumor of Mullerian versus non-Mullerian origin. This may have important implications in cases when the primary lesion is unknown since the therapy for ovarian and renal malignancies differs. Histological subtype specific aberrations in cyclin/Cdk expression may be important implications in the potential success of future therapies targeting Cdks. The first generation of these inhibitors are being evaluated in clinical trials. The second specific aim will evaluate steroid hormonal regulation of cyclin E using an in vitro model. The effects of estrogen and progesterone on cyclin E activity will be assessed using an ovarian cancer cell line. Increasing evidence suggests a role for hormones in the etiology of gynecologic malignancies. Moreover, cyclins have been shown to be regulated by estrogen and progesterone in breast cancer cell lines. The role of hormones in the development of reproductive tract cancer has important implications in the treatment of menopause and may also contribute to the direction of future therapeutic and preventative agents. Specific aim three will evaluate the expression and activity of cyclin dependent kinase inhibitors in order to elucidate the mechanism of aberrant cyclin E activity. The activity of a cyclin/Cdk is dependent upon the association with cyclin dependent kinase inhibitors (CdkIs). This specific aim will attempt to correlate cyclin E activity with the CdkIs, p2 1 and p27 in gynecologic malignancies. In addition, the role of estrogen and progesterone on CdkI association with cyclin E will be determined. Interestingly, it appears that the increase cyclin E activity in breast cancer cell lines in response to steroid hormones is mediated through alterations in the Cdk-inhibitory proteins. Understanding the mechanisms of cyclin E aberrations may lead to powerful and convenient models for studying potential tumor promoters, markers and antiproliferative agents.
CA77708	Greendale, Gail	2008	University of California, Los Angeles	Sex Steroids & Mammographic Density in the Postmenopause	Breast Exogenous Factors in the Origin and Cause of Cancer	DESCRIPTION (provided by applicant): Higher mammographic density is an independent risk factor for breast cancer and the magnitude of risk associated with mammographic density is greater than that associated with almost all other known risk factors for breast cancer. This application proposes to continue work in "Sex Steroids and Mammographic Density in the Postmenopause", a study of the effects of endogenous and exogenous sex steroids on mammographic percent-density. This study is an outgrowth of the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, which randomly assigned postmenopausal women to placebo, estrogen-only, or one of three combination estrogen/progestin treatments. To date, the principal findings of the "Sex Steroids and Mammographic Density Study" are: 1) Exogenous estrogen-only treatment did not affect mean mammographic density but significant increases in mammographic density did occur in 3 groups assigned to estrogen/progestin treatments; 2) In the three estrogen/progestin groups, but not in the estrogen-only group, the degree of increase in serum estrone level on-treatment predicted the amount of increase in mammographic density; and 3) Endogenous (pre-treatment) serum levels of estrone, estradiol, progesterone, and sex hormone binding globulin were positively associated with baseline mammographic density. Based on these findings, we propose to continue work in this study to gain a further understanding of variation in mammographic density, specifically: 1) What other factors are associated with baseline (pre-treatment) mammographic density? and 2) What additional factors predict increases in mammographic density during treatment? We hypothesize that hormones (in addition to those already studied), genetic polymorphisms in sex steroid biosynthetic/metabolic pathways, and genetic polymorphisms in sex steroid receptors will be related to baseline mammographic density and/or mammographic density response to treatment with hormone therapy. The proposed continuation project will last 4 years and will take place at UCLA and USC. Using stored samples, we will measure baseline and 12-month levels of prolactin and progestins. We will also extract DNA from stored samples to assess selected genetic polymorphisms. The mammographic density outcome data and all relevant covariates have already been measured during our prior work. We will quantify the relations between the hormone and genetic exposures measured in this project and mammographic density (at baseline as well as change in density between baseline and 12 months).

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CA79024	Sklar, Charles	2003	Sloan-Kettering Institute for Cancer Research	Premature Menopause in Survivors of Childhood Cancer	All Cancers Patient Care and Survivorship Issues Surveillance	DESCRIPTION: (Applicant's Description) Advances in the treatment of childhood cancer have resulted in markedly improved survival rates. However, with these advancements, cancer survivors now face the long-term consequences of treatment with intensive, multimodality therapies. While the majority of prepubertal girls and adolescent females retain or recover ovarian function during or immediately after completing cancer therapy, preliminary data indicate that many of these young women are at risk for premature menopause in the future. We propose to study, in a cohort of young adult survivors of cancer diagnosed during childhood/adolescence, the prevalence of early menopause, risk factors for the development of early menopause, the impact of an early menopause on quality of life and psychosexual functioning. The study cohort will consist of 5,500 young adult female survivors of cancer diagnosed during childhood and adolescence, selected from a larger population of survivors of childhood cancer, the Childhood Cancer Survivor Study (CCSS), and 3,000 sibling controls. Data will be collected using a self-administered questionnaire and will include the following topics: menstrual history and menopause status, covariates of menopause, health-related outcomes associated with premature menopause, and standardized instruments which measure quality of life and psychosexual functioning. Detailed information concerning cancer diagnosis and treatment, including cumulative drug dosages and radiation fields/doses, will be known for all study participants, facilitating the study of end-points of interest. The large size of the study population, the heterogeneity of diagnoses and exposures, combined with the extensive treatment data, will allow assessment of interaction between the major risk factors of interest.
CA80625	Cohen, Susan	2003	Yale University	Menopausal Symptom Relief for Women with Breast Cancer	Breast Cancer Complementary & Alternative Treatment Approaches Patient Care & Survivorship Issues	The proposed randomized, placebo-controlled clinical study will examine the use of acupuncture for menopausal symptom management for women who experience menopause following treatment for breast cancer. The study is designed to: 1) Test the anticipated treatment benefit for menopausal symptom relief using changes in frequency and severity of hot flashes as outcome measures; 2) Explore the anticipated treatment benefit of acupuncture for menopausal symptom relief using changes in severity of mood changes, sleep disturbances, loss of concentration, joint pain, headache and nervousness as well as changes in luteinizing hormone (LH), follicle stimulating hormone (FSH) and quality of life; 3) Determine the feasibility of the treatment strategy and develop realistic protocols for women previously diagnosed and treated for breast cancer by examining recruitment and retention rates and through exit interviews regarding the potential burden associated with symptom frequency and severity ratings and acupuncture sessions. A three group design (site specific needling, control needling, usual care) will be used. Acupuncture treatment will take the form of either menopausal specific acupuncture sites or control needling at acupuncture points identified in the literature as irrelevant to the symptoms associated with menopause. The non acupuncture control group will receive usual care with standardized educational information drawn from published menopausal literature concerning non-hormonal menopausal symptom management strategies. The study variables are Menopausal Symptoms with hot flashes (primary marker), mood changes, sleep disturbances, loss of concentration, joint pain, headache and nervousness as measured by the daily Symptom Diary and modified Kupperman Index; Physiological Measures of menopausal status (serum LH and FSH); Quality of Life as measured by The Menopause Specific Quality of Life Questionnaire; and Protocol Design as measured by recruitment and retention rates and exit interviews. A convenience sample of 81 women who experience menopausal symptoms within one year following treatment for Stage I or II breast cancer will be recruited. Data analysis includes descriptive statistics, repeated measures ANOVA, time series analysis and content analysis. Results from the study will test the effectiveness of acupuncture as a treatment for menopausal hot flashes and inform the design of a larger randomized, placebo-controlled clinical trial of acupuncture for menopausal symptom relief.

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CA80636	Weiss, Noel	2001	Fred Hutchinson Cancer Research Center	Endometrial Cancer and CYP1A1, GSTM1 and Polymorphisms	Endometrial Female Genital System Endogenous Factors in the origin and cause of cancer	DESCRIPTION: (Applicant's Description) Women who smoke cigarettes have about half the risk of endometrial cancer of non-smokers. Female smokers have been observed to have an increase in 2-hydroxylation of estrogens, and this increased 2-hydroxylation has been suggested as a mechanism to explain the apparent antiestrogenic effect of cigarette smoke. Polymorphisms in several genes involved in metabolizing potential carcinogens in cigarette smoke have been related to an increased risk of lung cancer. One of these genes is also involved in 2-hydroxylation of estrogens. Thus, it might be anticipated that women who have the high-risk genotypes, in terms of lung cancer, would have a reduced risk of a condition such as endometrial cancer, whose incidence is reduced by cigarette smoking. However, in a recent small case-control study, a strong, positive relationship between the presence of some of the polymorphisms in these genes and endometrial cancer risk was reported. In our proposed population-based case-control study, we will explore whether polymorphisms in some of these genes are associated with endometrial cancer risk. The genes of interest are: cytochrome P450 1A1 (CYP1A1), glutathione-S-transferases M1 (GSTM1) and T1 (GSTT1), and catechol-O-methyltransferase (COMT). Cases and controls will be drawn from our funded study of continuous combined hormone replacement therapy and endometrial cancer. Cases are women ages 50-69 years with incident endometrial cancer diagnosed between 6/l/97 and 7/31/00, who reside in western Washington. Controls are women recruited through random-digit dialing (ages 50-64 years) and Health Care Financing Administration files (ages 65-69 years), who reside in the same geographic area. In the proposed study, 175 cases and 175 controls will be asked to provide a blood specimen at the time of interview. Using purified DNA from these blood samples, the genotypes of interest will be assayed using PCR and RFLPs. Differences in the distributions of genotypes between cases and controls will be assessed in the whole study population, as well as in sub-groups of women defined by cigarette smoking history and use of hormone replacement therapy (HRT). Since endometrial cancer is strongly hormone-related, the results of this study could have relevance for other, more common cancers whose relation to hormones is not so straightforward. Additionally, this information potentially could be used to predict a woman's sensitivity to the carcinogenic effects of HRT, and thus bear on a woman's decision regarding long-term use of HRT.
CA80888	Carney, Patricia	2005	Dartmouth College	Hormone Replacement Therapy and Breast Cancer	Bone, Osteosarcoma/Malignant Fibrous Histiocytoma, Breast Exogenous Factors in the origin and cause of cancer	The long-term objective of this study is to evaluate the relationships between hormone replacement therapy (HRT) and breast cancer detection, breast cancer risk, breast tumor prognostic characteristics and health-related quality of life. Although the results of numerous case-control and follow-up studies suggest that hormone replacement therapy modestly increases breast cancer risk, most studies have been unable to adjust adequately for frequency of mammographic screening. This is an important limitation because more frequent use of mammography screening among women who maintain hormone replacement prescriptions through regular physician visits may lead to increased detection of breast cancer relative to women who do not use hormone replacement therapy. Our study design, which involves an existing cohort identified through the New Hampshire Mammography Network (NHMN) - a statewide, population-based mammography registry comprising more than 150,000 women - overcomes this limitation. Using a baseline survey, administered at the time of mammography, we have already obtained breast cancer risk factor information, including current HRT use, from all women in the NHMN registry. Through NHMN we have already identified 74,200 women who are pre- or post-menopausal including approximately 26,700 current HRT users. We will follow these women for four years prospectively to ascertain new cases of breast cancer. All NHMN enrollees have already provided permission to link medical, radiologic and pathology data, and consented to further contact for research purposes. We will implement a supplemental survey in Years 1 and 4 to obtain a detailed history of HRT use, additional risk factor information and health-related quality of life. All other data will be obtained from the well established NHMN. Our primary specific aims are to evaluate the impact of HRT on 1) mammography performance (i.e., sensitivity and specificity of screening mammography, proportion of uninterpretable mammograms and consequent use of other imaging procedures); 2) breast cancer incidence (especially combination therapies); 3) breast cancer tumor prognostic characteristics (e.g., TNM stage, tumor grade, axillary lymph node status and estrogen receptor status). As more women consider use of HRT to prevent osteoporosis and other diseases, understanding its impact on quality of life is imperative. Therefore, a secondary aim is to assess the impact of HRT on health- related quality of life. Results of the proposed study will benefit radiologists who interpret mammograms, and women and their health care providers, who must balance the complex issues of disease risk and health-related quality of life when deciding whether or not to use hormone replacement therapy.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
CA81212	Zeleniuch-Jacquotte, Anne	2002	New York University School of Medicine	Androgens and Cancer of the Endometrium	Endometrial Female Genital System Endogenous Factors in the Origins and Cause of Cancer	The hypothesis that estrogens unopposed by progesterone promote endometrial cell proliferation, and therefore increase risk of endometrial cancer, is supported by experimental as well as epidemiologic data. Because androgens are the main source of circulating estrogens in postmenopausal women, a positive association of circulating androgens with endometrial cancer risk is also expected. This study will be the first to assess the association of prediagnostic levels of circulating estrogens and androgens with endometrial cancer risk in postmenopausal women. The specific objectives of this project are to: (1) Assess the relation of postmenopausal endogenous estrogens with endometrial cancer risk in a case-control study nested within three prospective cohorts: the New York University Women's Health Study (NYUWHS), the ORDET Study in Milan, Italy, and the Northern Sweden Health and Disease Study in Umea, Sweden; (2) Assess the relation of postmenopausal endogenous androgens with endometrial cancer risk in the same case-control study. For all three cohorts, serum samples collected at enrollment and stored at 80oC are available for biochemical analyses. A case-control study of endometrial cancer and postmenopausal endogenous estrogens nested within the NYUWHS and funded by the NCI (R29 CA66189, PI: A. Zeleniuch- Jacquotte) is already ongoing. The design of this study will be implemented in the two other cohorts. All incident cases diagnosed within the studies will be included. Individually-matched controls will be selected among all subjects from the same cohort with the following characteristics: postmenopausal at entry, alive, free of cancer and with an intact uterus at the time of diagnosis of the case, and matching the case on age at enrollment (+6 months), and date of enrollment (3 months). As is currently done for the NYUWHS participants, data on potential confounders will be collected through telephone interviews for Umea and ORDET participants. Serum samples of all cases and matched controls will be assayed in the same laboratory for estradiol, free-estradiol, estrange, testosterone, androstenedione, DHEA, and SHBG. Combining cases from the three cohorts will result in a total of 140 cases, a much larger number than would be expected in each individual cohort.
CA81220	Johnson, Christine	2005	Case Western Reserve Univ-Henry Ford Health Sciences Center	Colon Cancer Survivors--Medications & Risk of Recurrence	Colon and Rectal Gastrointestinal Tract Patient Care and Survivorship Issues	Colorectal cancer will be diagnosed in over 129,000 Americans in 1999. To combat this disease, new avenues to decrease the risk of colorectal cancer, such as chemoprevention, are being explored by researchers. Non-steroidal anti-inflammatory drugs (NSAIDs) and hormone replacement therapy (HRT) have been shown to decrease incident colon cancer. Little is known of their effect on persons with a history of colon cancer which, fortunately, is a continually expanding population as survival has been significantly improving over the last twenty years. The objective of this epidemiologic study is to determine whether NSAIDs or HRT is associated with recurrence or survival among individuals diagnosed with colorectal cancer. The proposed research will establish a cohort of colorectal cancer patients treated with curative intent and create a comprehensive longitudinal database, including data on the ascertainment of subsequent adenomatous polyps, colorectal cancer and survival. The specific aims are: (1) to determine whether NSAID use deceases the risk of recurrence of colorectal cancer; (2) to determine whether HRT use deceases the risk of recurrence of colorectal cancer; (3) to determine whether NSAID use affects short-term survival; and (4) to determine whether HRT use affects short-term survival. The cohort will be established from colorectal cancer patients enrolled in two managed care organizations, Health Alliance Plan (Detroit, MI) and Health Partners (Minneapolis, MN). Cohort subjects will be followed for at least five years for new evidence of disease, recurrence and survival outcome. Using automated pharmacy data, the timing of use and exposure to NSAIDs and HRT will be analyzed among cancer survivors, along with potentially confounding variables, in relation to these outcomes.
CA81243	Spink, David	2003	Wadsworth Center	Carcinogenicity of B Ring Unsaturated Estrogens	Breast Cancer-Related Biology Endogenous Factors in the Origin and Cause of Cancer	The major concern regarding estrogen replacement therapy (ERT) is the significant increase in the risk of breast cancer that accompanies long-term use. The most commonly used formulation for ERT is Premarin, a preparation consisting largely of B-ring unsaturated estrogens including conjugated forms of equilin (Eq) and equilenin (Eqn). Our preliminary studies show Ah-receptor-regulated metabolism of Eqn to 4-hydroxylated metabolites in several human breast-derived cell lines expressing cytochrome P4501B1 (CYP1Bl). Semiquinones and quinones derived from these 4-hydroxy metabolites, which are adductive and lead to free radical production, may be involved in carcinogenesis. We hypothesize that estrogens are involved in both the initiation and promotion phases of carcinogenesis, and that aromaticity of the B-ring of steroidal estrogens increases carcinogenic potency. Our broad, long-term goal is to determine whether steroidal estrogens, including the B-ring unsaturated estrogens, Eq and Eqn, are carcinogenic through metabolic activation via catechol estrogens. 0ur Specific Aims are to: 1) Characterize Eq and Eqn metabolism in a series of immortalized tumor- and non-tumor-derived human breast-cell lines. Pathways of Eq and Eqn bioactivation involving hydrolysis of conjugates, reduction to 17beta-dihydro forms and hydroxyation to catechol estrogens will be investigated. 2) Determine the catechol synthetic activities of human cytochromes P450 of the CYP1, CYP2, and CYP3 families with Eq, Eqn, and their 17alpha- and 17beta-dihydro forms as substrates. 3) Establish transgenic mouse lines expressing human CYP1B1 in the mammary epithelium, 4) Determine the effects of treatment with Eq and Eqn on DNA damage and the incidence of mammary-gland tumors in human CYP1B1-transgenic mice. The studies described here will provide novel results regarding the metabolism of the B-ring unsaturated estrogens by human enzymes in breast epithelial cells, and may provide mechanistic data supporting a role of metabolic activation of Eq, Eqn, and endogenous in the initiation of carcinogenesis in the human breast.

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CA85913	Daling, Janet	2005	Fred Hutchinson Cancer Research Center	HRT Use and Risk of Lobular and Ductal Breast Cancer	Breast Cancer Cancer-Related Biology Exogenous Factors in the Origin and Cause of Cancer	Incidence rates of invasive lobular breast carcinomas (ILBC) have increased steadily in the United States since 1977, whereas the trend of increasing incidence of ductal breast cancer has plateaued since 1987. This rise in lobular tumors has occurred specifically among women over age 50. The use of combined estrogen-progestin hormone replacement therapy (CHRT) has also risen steadily over this time period, and recent analyses from two case-control investigations suggest that postmenopausal women who use CHRT may have an increased risk of ILBC, whereas there is no relationship of CHRT to ductal cancer. Few epidemiologic studies have assessed how known or suspected risk factors for breast cancer differ across different histologic types, but such investigations are important because there are likely to be multiple pathways leading to the development and progression of breast cancer of different histologic types. The primary objectives of this proposed study are to confirm recent preliminary findings that CHRT is associated with lobular breast cancer in a large population-based study, to assess this relationship in greater detail, and to explore mechanisms for this association. We propose to conduct a case-control study of 900 women aged 55-79 who have been diagnosed with breast cancer (450 lobular, 450 ductal) and 450 population-based controls who reside in the three county Seattle-Puget Sound metropolitan area of western Washington. The specific questions to be addressed are: (1) Is the use of CHRT associated with an increase in the incidence of invasive lobular breast cancer in women aged 55-79. (2) Is the use of CHRT associated with an increase in the incidence of invasive ductal breast cancer in women aged 55-79? (3) Do the duration, patterns and/or recency of CHRT use influence he size of the association? (4) Is the use of CHRT associated with alteration in the histologic characteristics, tumor cell proliferation, or expression of steroid hormone receptors, oncogenes, and cell cycle and cell death regulator proteins of lobular and ductal breast cancers?
CA87538	Rossing, Mary	2007	Fred Hutchinson Cancer Research Center	Epidemiology of Ovarian Cancer: New Hypotheses	Female Genital System Ovarian Exogenous Factors in the Origin and Cause of Cancer	Much of the previous epidemiologic research on ovarian cancer has been conducted within the conceptual with conceptual framework of the ovulation and gonadotropin. However, additional mechanisms must be operative to account for epidemiologic findings regarding this disease. In this study, we will address the hypothesis that progesterone reduces risk of epithelial ovarian cancer. We will examine the relation of exogenous progestins administered as a component of hormone replacement therapy (HRT) with disease risk. We will further assess whether sunlight and dietary sources of vitamin D influence risk. The study will contribute to a better understanding of pathogenic mechanisms of epithelial ovarian cancer, and may provide information leading to new means of reducing the occurrence of this disease. We propose to conduct a population-based, case-control study of epithelial ovarian cancer among women aged 35-74 years residing in thirteen counties of Washington State. Cases will be identified through a population-based cancer registry operating as part of the Surveillance, Epidemiology and End Results Program. Controls will be identified through random digit telephone dialing, and will be selected to be similar in age and area of residence to cases. In-person interviews will be conducted and blood samples will be collected. The findings of this study will have appreciable public health importance. Study of the impact of different HRT regimens, particularly estrogen/progestin combinations, on ovarian cancer risk has been deemed an urgent task for research. Recent calls for reappraisals of the risk/benefit ratio of unopposed estrogen and combined estrogen/progestin HRT highlight the need to understand the relation of these medications with ovarian cancer risk, and to incorporate this knowledge into risk/benefit considerations.
CA87969	Colditz, Graham	2004	Brigham And Women's Hospital	Dietary and Hormonal Determinants of Cancer in Women	Breast Cancer Colon and Rectal Cancer Gastrointestinal Tract Genital System, Female Ovarian Cancer	Using repeated measures of exposure and the long follow-up in the Nurses' Health Study (1976 to 2004), we propose a series of analyses relating specific aspects of diet, nutritional status, and postmenopausal use to breast cancer incidence and survival among women with breast cancer. DNA samples from cohort numbers will be used to evaluate associations between functional important polymorphisms and risk of breast cancer and potential gene-diet interactions. Specific exposures will also be related to tumor characteristics using pathology blocks that have been collected from incident breast cancer cases. Dietary hypotheses include that low folate intake and blood levels increase breast cancer risk, in particular tumors characterized by negative estrogen receptor status and aberrant methylation of the genes for this receptor and p16; that dietary fiber and specific types and sources of fiber, flavonoids, overall antioxidant intake, conjugated linoleic acid (CLA), and decreases in adiposity each reduce risk. We further hypothesize that high dietary glycemic load and intakes of heterocyclic amines from cooked meat, N-3 fatty acids from fish, and (after a long latent period) total fat each in increase risk. Polymorphisms in genes related to specificity dietary exposures (MTHFR, manganese SOD, and NAT1/2) will be examined in relation to breast cancer directly and as interactions with the corresponding dietary factors. We also propose to evaluate the type and dose of post-menopausal hormone preparations in relation to overall risk of breast cancer and estrogen receptor status of tumors. Finally, we hypothesize that high intake of dietary fat reduces survival among women with breast cancer, but that high intake of protein, regular physical activity, and avoidance of weight gain each increase survival. Because of the prospective design with repeated measures of exposure, long follow-up, and large numbers of breast cancer cases (over 5,000 cases for most dietary analyses), these analyses will provide important data for women and their health providers attempting to reduce risk of breast cancer.

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CA89393	Iglehart, James	2005	Dana-Farber Cancer Institute	Plasma estrogens in breast cancer risk and prevention	Breast Chemoprevention Technology and/or Marker Evaluation with Respect to Fundamental Parameters of Method Technology and/or Marker Testing in a Clinical Setting	A large body of epidemiologic evidence has consistently linked reproductive factors to breast cancer risk. Ages at menarche and first pregnancy are parameters in established breast cancer risk models/-1-3. Obesity and hormone replacement therapy also increase postmenopausal breast cancer risk/4. SERMS, such as tamoxifen and raloxifene, not being widely prescribed to reduce breast cancer risk/8. This is due to perceptions about side effects and the inability to identify those women who most benefit from tamoxifen. We and others have shown that postmenopausal levels of serum estrogens are highly correlated with breast cancer risk 9,10. Strategies of estrogen deprivation are increasingly prominent among the various therapeutic hormonal interventions used for hormone receptor positive tumors. In postmenopausal women, adjuvant chemical or surgical oophorectomy may improve survival/11. In postmenopausal women, agents that inhibit aromatase, the critical enzyme in conversion of precursors to estrogen reduce estrogen levels in the circulation, breast tissue, and tumors 12. Currently available aromatase inhibitors are highly selective and substantially reduce circulating estrogen levels without altering other aspects of steroid production 13. They are effective in the treatment of metastatic disease, and a large adjuvant trial is in progress. The goal of this project is to improve breast cancer prevention by translating these observation into clinical practice. In aim one, we will test the hypothesis that by incorporating data on serum estrogen levels and mammographic density from the Nurses' Health Study we can improve current models of individual breast cancer risk. In the second aim, we will develop a novel paradigm for breast cancer prevention among postmenopausal women at increased risk of high levels of circulating estrogens. We will assess whether an aromatase inhibitor is sufficiently well tolerated (by its effects on bone density, menopausal symptoms and blood lipids) to permit further development for chemoprevention. If successful, these studies will contribute to the adoption of quantitative paradigm of breast cancer risk estimation and reduction that more closely parallels the widely accepted models of cholesterol and blood pressure titration that have transformed cardiovascular disease in the US.
CA89552	Habel, Laurel	2006	Kaiser Foundation Research Institute	Mammographic Denisity in a Multi-Ethnic Cohort	Breast Exogenous Factors in the Origin and Cause of Cancer	Mammographic density is one of the strongest known risk factors for breast cancer, yet it has been described as among the most undervalued and underutilized factors in studies of breast cancer etiology. While recently there has been interest in the potential value of mammographic density as an intermediate marker of breast cancer risk, several questions remain unanswered. A needed area of research is the identification of risk factors for breast cancer that are related to mammographic density, and may therefore act through a causal pathway reflected directly or indirectly by this feature. The aim of this study is to identify factors that are associated with mammographic density, with a special focus on race/ethnicity, circulating hormones (e.g., estradiol, progesterone, testosterone, sex hormone-binding globulin), bone mineral density, and modifiable factors such as diet (e.g., phytoestrogen, percent calories from fat,) and physical activity (e.g., recreational activity, occupational activity, and household activity). We will also look at how density changes as women transition through the menopause. This proposal seeks funding for obtaining and assessing mammograms on approximately 178 Chinese, 209 Japanese, 102 African-American, and 498 Caucasian women participating in SWAN (Study of Women's Health Across the Nation). We will request all mammograms performed as part of routine care during the SWAN follow-up period and request that women have a mammogram within six months of follow-up exam six. SWAN is a multi-site population-based study designed to investigate the menopausal transition in women of diverse ethnicities. At baseline and six annual follow-up exams, data are collected on a wide range of factors, including detailed anthropometry, bone mineral density, menstrual information (e.g., monthly calendars), and complete reproductive histories. In addition, blood is drawn, timed to the luteal phase of the menstrual cycle, for hormone analyses. An expert in assessing mammographic density will measure total area of the breast and area of dense tissue (for percent density) and classify mammograms according to parenchymal pattern (Wolfe system). This mammography information will be merged with data from SWAN to create analytic files. Repeated measures regression analysis will be used to examine the association between factors of interest and mammographic density. The SWAN study population provides a unique opportunity to efficiently examine the relationship between several established and suspected risk factors for breast cancer and mammographic density. The results will improve our understanding of a number of breast cancer risk factors and help determine whether mammographic density should be considered as a potential intermediate marker of breast cancer risk for intervention studies of several modifiable factors.

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CA89617	Pollard, Jeffrey	2005	Yeshiva University	Progesterone, Cell Cycle and Cancer	Breast Endometrial Female Genital System Endogenous Factors in the Origin and Cause of Cancer	Estrogens are the major carcinogen in the environment of most females with exposure to unopposed estrogen increasing the risk of breast and endometrial cancer. Conversely, it has become increasingly apparent that estrogens are essential for the well being of women (and men) throughout life. Progesterone acts to oppose the effects of estrogen on cell proliferation and, consequently, it is used in the treatment of endometrial cancer and it is an essential component of hormone replacement therapy designed to alleviate post-menopausal symptoms in women. It is, therefore, of fundamental importance to understand the mechanism of action of these hormones on cell proliferation. In adult ovariectomized mice, a single injection of estradiol-17beta (E2) results in the stimulation of a wave of DNA synthesis and cell proliferation that is restricted to the uterine epithelium. This proliferation is completely inhibited by pretreatment with progesterone (P4). The uterine epithelium can be isolated with great purity in a state suitable for biochemical analysis. This method together with defined hormonal regimens provides a controllable model in which to study the mechanism of action of these hormones in vivo. In tissue culture cells the cell cycle is regulated by the orderly activation of cyclins and their dependent kinases (Cdk). These include the cyclin D-Cdk4 and cyclin D-Cdk6 complexes acting early in G1 and the cyclin E-Cdk2 complex acting at the G1 to S-phase boundary. Our studies in the uterine epithelium have shown that E2 induces the re-localization of cyclin D1 and Cdk-4 to the nucleus and, results in orderly activation of cyclin-E and cyclin ACdk-2 activities and hyper-phosphorylation of pRb and p107. Progesterone pre-treatment prohibited the cyclin D1/Cdk-4 relocalization to the nucleus with a consequent inhibition of pRb and p107 phosphorylation. In addition, P4 abrogated the E2 induced cyclin E and cyclin A-Cdk2 activities. The specific aims of this grant are: 1) To determine the mechanism whereby P4 prohibits cyclin D1/Cdk4 nuclear accumulation following E2 treatment; 2) To determine the mechanism of action of P4-inhibition of Cdk-2 activation; 3) identify differentially regulated genes in the uterine epithelium following E2 treatment in the presence and absence of P4; 4) to develop methods to interfere with signaling pathways in the uterine epithelium in vivo. It is expected that by the end of the grant that the mechanisms of cyclin D1/Cdk4 exclusion can be identified and novel proteins associated with this process isolated. Furthermore, novel E2 and P4-regulated genes that play important roles in the control of epithelial cell proliferation should be identified. These studies will define specific mechanisms that may result in the development of therapeutics that would inhibit estrogen's mitogenic effects in tumors as well as in benign proliferative diseases such as endometrial polyps and endometriosis.
CA89750	Zeleniuch-Jacquotte, Anne	2003	New York University School of Medicine	Serum Lignan and Risk of Endometrial Cancer	Endometrial Female Genital System Exogenous Factors in the Origin and Cause of Cancer	There is strong experimental and epidemiologic evidence that estrogens unopposed by progesterone increase the risk of endometrial women. Because of their anti-estrogenic properties (through aromatase inhibition and increase of SHBG synthesis) and possible tumor growth inhibition properties, it has been proposed that ligands may protect against hormone-related cancers, in particular breast and endometrial cancers. The specific aim of this study is to assess whether serum levels of the main human ligand, enterolactone, are negatively associated with risk of endometrial cancer. The study will use the resource of an ongoing case-control study of endometrial cancer and endogenous androgens and estrogens, nested within 3 cohorts, the New York University Women's Health Study (NYUWHS) in New York, United States, the Northern Sweden Health and Disease Study (NSHDS) in Umea, Sweden, and the ORDET Study in Milan, Italy. This ongoing study is funded by NIH. Case subjects are all incident cases of endometrial cancer diagnosed within appropriate parent study dates. Two controls matching the case on parent cohort, menopausal status, age at enrollment (+/-6 months), and date of enrollment (+/-3 months) will be selected. Data on known risk factors are available. Serum samples (for the NYU WHS and the ORDET Study) or plasma samples (for the Umea Study) collected at the time of enrollment in the cohort, and stored at 300 C are available for biochemical assays. The assays will be performed in Finland by Dr. Adlercreutz, who developed, the assay methodology. It is expected that approximately 300 cases will be eligible for the study. The availability of this ongoing study offers a unique opportunity to address the specific aim rapidly and at a minimal cost.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
CA90440	Gupta, Chanda	2006	University of Pittsburgh at Pittsburgh	Role of Estrogens in Development of Lung Cancer	Lung Endogenous and Exogenous Factors in the Origin and Cause of Cancer	This project is a sub-project of the SPORE in Lung Cancer (PI: Siegfried, Jill) Increasing evidence is emerging that women are more susceptible to lung cancer than men, suggesting a role for estrogen in the development of the disease. Estrogens are known to act as tumor promoters, through a receptor-mediated mechanism in reproductive organs. These are some reports of estrogen receptor expression in lung tumors, and it is possible that the lung is an estrogen-responsive organ. Recent findings that early menopause is associated with a reduced lung cancer risk and that use of estrogen replacement therapy results in an increased incidence of lung cancer supports this speculation. Additional support for this hypothesis comes from our recent studies, which identified much higher expression of both estrogen receptor5 (ER) alpha, and in some cases ERbeta, in non- small cell lung tumor cells that in normal bronchial epithelial ells or fibroblasts from the lung. Estrogen induced increased cell growth in lung tumor cell lines in vitro and this effect was blocked by the anti-estrogen ICI 182,780. Estrogen also enhanced growth of the lung tumor cell line H23 in immunocompromised mice. Tamoxifen, an inhibitor of estrogen, reduced the in vivo growth of the lung tumor by itself, but enhanced it in the presence of estrogen, suggesting tamoxifen may be a partial agonist in the lung, as it is the uterus and bone. Based on these findings, we hypothesize that estrogen plays a direct role in promoting lung cancer through a receptor mediated mechanism and may be responsible for at least some of the increased risk of women to lung cancer. Estrogenic effects may also help explain the high proportion of women among non- smokers who are diagnosed with lung cancer. PROJECT One of this SPORE application found that expression of the Gastrin-Releasing Peptide Receptor (GRPR) gene was associated with a diagnosis of lung cancer in non-smoking women, and that GRPR expression was enhanced by estrogen in lung cells expressing the ERbeta. This suggests a mechanistic link between estrogen and lung cancer risk. In Project Two of the SPORE, we will examine the role of estrogen in more depth. The Specific Aims are: (1) Determine the frequency and level of expression of the ERalpha and ERbeta in lung tumors and normal lung tissues; (2) examine ability of estrogens to enhance tumor cell proliferation in vitro and in vivo, and ability of anti-estrogens to oppose this effect; (3) determine relative mRNA expression levels of the ERs in biopsies of the human airway of normal and pre-neoplastic histology from current and former smokers; (4) determine effects of estrogen on expression of three genes important in lung cancer proliferation; and (5) examine in on-going clinical trials, and in female subjects from Project one, whether estrogens influence lung cancer risk.
CA90579	Boyd, Norman	2003	Ontario Cancer Institute	Effects of Diet on Growth Hormone-IGF-1 Axis	Breast Nutritional Science in Cancer Prevention	The specific aim of this proposal is to determine whether In premenopausal and postmenopausal women blood levels of Insulin like Growth Factor-I, Insulin like Growth Factor Binding Protein -3 and Growth hormone are influenced by a low-fat high- carbohydrate diet. The general method to be employed will be to perform assays for growth factors and hormone on blood samples, and nutrient analysis of food records, collected from subjects taking part in our ongoing multicentre randomized dietary intervention trial. This trial is designed to test the hypothesis that intervention with a low-fat high-carbohydrate diet will, in women with extensive mammographic densities, over a 10 year period reduce the incidence of breast cancer by 29 percent. The trial is explanatory in that it seeks to determine if there is a biological effect of dietary fat reduction in terms of a reduction in breast cancer incidence. To meet this goal we have selected as participants highly motivated subjects who are at increased risk of breast cancer, we have provided them with a high level of assistance in making a dietary alteration, we follow them carefully to ensure the maintenance of dietary change and the correct identification of subjects who develop breast cancer, and we plan to analyse the results according to study group and dietary compliance. Recruitment of the 4615 subjects required for the trial was completed in November 1998. (A total of 4693 were randomized). Blood samples and food records from subjects enroled in the trial will be used to test the hypotheses given below about the effects of dietary intervention on growth factors and hormones associated with breast cancer risk. Modulation of these factors by dietary intervention would indicate potential mechanisms by which diet may influence risk of breast cancer. Although not the purpose of the research proposed here, the long term nature of the trial, the complete follow-up of all subjects, and the complete ascertainment of breast cancer, will ultimately allow any changes in blood markers found in the present research to be examined in relation to changes in breast cancer incidence.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
CA91019	Ross, Ronald	2006	University of Southern California	Genes and the Estrogen Effect on Endometrial Cancer	Endometrium Female Genital System Interactions of Genes and/or Genetic Polymorphisms with Exogenous and/or Endogenous Factors	The etiology of endometrial cancer is relatively well understood. Estrogen stimulation of the endometrium without the modulatory effects of progestins is the major cause. Estrogen replacement therapy (ERT) in menopause and obesity are the principal risk factors. The effect of the latter is probably due to the association between postmenopausal obesity and circulating bioavailable estrogen levels. Oral contraceptives and pregnancy, both of which deliver estrogen stimulation to the endometrium but with the continuous modulatory influence of progestins, are associated with reduction in risk. Combination hormone replacement therapy in which a progestin is added to estrogen for all or part of the monthly cycle results in no increase in endometrial cancer risk over that of a non-user of hormone replacement. Despite the fact that ERT and obesity are the major risk factors, only a small proportion of women using ERT or even with extreme obesity will develop endometrial cancer. It would be important from a public health as well as from a mechanistic view to be able to predict which women those will be. We propose to evaluate a series of eight candidate genes (CYP17, CYP19, HSD17B1, ER, CYP1A1, CYP1B1, COMT andPR) in the estrogen biosynthesis, transactivation and metabolism pathways to determine if the effects of these risk factors might be mediated or modified by genetic variability. We will evaluate this question in the context of a prospective epidemiologic study of 133,000 female California teachers (the California Teachers Study) using a nested case-control design. We will also examine in detail the possible impact of phytoestrogens on endometrial cancer risk reduction in conjunction with HRT, obesity and the eight candidate genes under evaluation.
CA93772	Sillman, Rebecca	2006	Boston Medical Center	Breast Cancer Treatment Effectiveness in Older Women	Breast Patient Care and Survivorship Issues	DESCRIPTION (provided by investigator): An estimated 192,200 women were diagnosed with breast cancer in 2001, more than half of whom were 60 years of age or older. Of concern is that while breast cancer-specific mortality rates have declined among women less than 70 years old, they are either stable (70-79 year olds) or are increasing (80+ year olds) among those 70 years or older. One explanation for this is that older women receive less than standard therapy more frequently than younger women. Neither efficacy nor effectiveness data to date justify this pattern of care. Taking advantage of the Health Maintenance Organization (HMO) Cancer Research Network, we propose to conduct a historical cohort study of an unselected group of older women (>65 years of age) newly diagnosed with early stage breast cancer (stages I-II) between 1990 and 1994. Specifically, we will (1) Compare the effectiveness of standard primary tumor therapy (breast conserving surgery, axillary dissection, and radiation therapy or modified radical mastectomy) versus other than standard therapy in preventing breast cancer recurrences and mortality, adjusting for co-morbidity, tumor characteristics, geographic site, and demographic characteristics; (2) Determine the extent to which the addition of systemic adjuvant therapy (chemotherapy, hormonal therapy, or the combination of chemotherapy and hormonal therapy) modifies the effectiveness of standard and other than standard primary tumor therapy in preventing breast cancer recurrences and mortality; (3) Describe patterns of surveillance testing for breast cancer recurrence and determine the extent to which surveillance testing is associated with a reduction in breast cancer-specific mortality; and (4) Identify provider, tumor, and patient characteristics associated with the receipt of standard primary tumor therapy and systemic adjuvant therapy in older women with newly diagnosed early stage disease in the HMO setting. Six sites from throughout the United States will together identify and follow 2180 women for ten years. Both electronic and medical record data sources will be used to collect information that will allow us to characterize the separate and joint effects of treatment, tumor, and patient characteristics on breast cancer recurrence and mortality. Findings from this study will inform clinical practice, particularly the care of older women with co-morbidities who are unlikely to participate in clinical trials.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
CA94745	Rossing, Mary	2004	Fred Hutchinson Cancer Research Center	Use of Antidepressants and Risk of Breast Cancer	Breast Exogenous Factors in the Origin and Cause of Cancer	Diagnosis of depression is increasing in the United States, and women are twice as likely as men to suffer from depressive symptoms. With the advent of the selective serotonin reuptake inhibitors (SSRIs), antidepressant use has increased dramatically during the 1980s and 1990s, and the types of antidepressants prescribed have changed. Recent evidence that antidepressants can reduce the occurrence of menopausal hot flashes has led to predictions that antidepressant use may increase still further, particularly among women who are reluctant to take hormone replacement therapy due to concerns about breast cancer risk. Thus, better understanding of any possible role of antidepressants in breast cancer etiology is of substantial and growing public health importance. Initial concern about a role of antidepressants in human carcinogenesis was sparked by reports of increased occurrence of mammary tumors in rats administered tricyclic antidepressants or SSRIs. Epidemiologic findings have been inconsistent, but have not dispelled this concern. Two recent studies reported an elevated risk of breast cancer among users of some antidepressants; however, the class or type of antidepressant associated with increased risk differed. These studies were limited by the potential for error in self-reported drug use, and by relatively small numbers of exposed women. We propose to conduct a population-based, case control study to examine the association between antidepressant use and risk of breast cancer within the Group Health Cooperative of Puget Sound (GHC). Approximately 3,652 women diagnosed with first primary breast cancer (3,080 with invasive disease) during 1990-2000 and 7,304 randomly selected, matched controls will be included. Antidepressant use will be ascertained through the GHC pharmacy database, and information on potential confounding factors will be obtained from risk factor surveys routinely administered by GHC. The large study size and broad, recent interval of diagnosis years of cases will allow examination of the type, timing, and duration of use of antidepressants overall, classes of drugs (e.g., SSRIs or tricyclics), and individual drugs such as fluoxetine and paroxetine. Use of the pharmacy database will provide unbiased and complete exposure data relative to previous studies based on self-reported drug use.
CA95113	Modugno, Francesmary	2004	University of Pittsburgh at Pittsburgh	Serum Markers of Breast/Ovarian Cancer Risk	Breast Ovarian Female Genital System Endogenous and Exogenous Factors in the Origin and Cause of Cancer	Both breast and ovarian cancers are costly in terms of morbidity and mortality to women. While both diseases have some well-defined behavioral risk factors, there are few, if any, established biomarkers of risk. Moreover, there are a paucity of markers that have the possibility to be applied in a clinical setting, and there is a lack of prospectively collected data and serum samples available to researchers to explore new risk markers. Such markers, tested in a large, prospective setting, are urgently needed in order to identify women at an increased risk for these diseases, as well as to improve our models of risk assessment and to devise effective prevention strategies. We have formed a multi-institutional consortium linked to an ongoing multi-center trial in order to evaluate prospectively the utility of serum biomarkers as risk factors for breast and ovarian cancers. In particular, we will (1). determine prospectively the effects of serum markers of estrogen metabolism, body mass index (BMI), and hormone replacement therapy (HRT) on postmenopausal breast cancer risk; and (2). determine prospectively the association of insulin related serum biomarkers on postmenopausal ovarian cancer risk. To achieve our objectives, we will undertake two nested case-control studies within the Observational Study (OS) of the Women?s Health Initiative (WHI), a multi-center prospective study of women?s health funded by the NIH. The first study will compare BMI, HRT and estrogen metabolite levels in WHI banked serum between 200 confirmed cases of invasive breast cancer and 200 healthy women frequency matched by age, race and study site. The second study will compare insulin, glucose and insulin-like growth factor levels in WHI banked serum between 200 confirmed cases of epithelial ovarian cancer and 200 healthy women frequency matched by age, race, study site and HRT status. Risk factor, confounding and outcomes data has already been collected and verified by the WHI Clinical Coordinating Center and will be provided to us in a clean study database. All laboratory assays will be performed by experienced, collaborating investigators with whom we have worked in the past. Justification for our studies comes from preliminary data we have generated. Approval to undertake this collaboration has already been obtained from the WHI. By the end of this project, we will have prospectively evaluated some new and promising serum markers of risk for breast and ovarian cancer. We also expect to identify additional related research questions, which we anticipate studying further in a multi-center, collaborative fashion within the various arms of the WHI.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
CA95717	Porter, Peggy	2006	Fred Hutchinson Cancer Research Center	Molecular Alterations in Lobular/Ductal Breast Cancer	Breast Exogenous Factors in the Origin and Cause of Cancer	Lobular breast cancers differ both morphologically and clinically from the more common ductal type. They also differ in steroid hormone receptor expression and proliferation rates. Breast cancer cells demonstrating a lobular morphology may also be distinct with respect to allelic loss patterns and components of defined pathway, such as e- cadherin/catenin and BRCA1/BRCA2-mediated DNA repair. It has been difficult to assess the unique characteristics of lobular cancer most studies can only evaluate a small number of this relative uncommon tumor type. Over 350 tissue samples each of invasive lobular and ductal breast cancer will be collected and tested for expression of breast cancer- related proteins as part of an NCI-funded case-control study to assess associations between the use of combined hormone replacement therapy (CHRT) and the incidence of both invasive lobular and ductal breast cancer in women aged 55-79. Using the tissue samples collected in the study, we propose to 1) evaluate the difference in the rates of p53 allelic loss, mutation and protein over-expression in 350 each of invasive lobular and ductal cancers and 2) evaluate the difference in the genome- wide rate of allelic loss in 100 each of lobular and ductal cancers using newly developed microarray techniques (HuSNP). The large amount of data that is being carefully collected as part of the parent study will also allow us explore the contribution of alterations in BRCA-related DNA repair components and e-cadherin abnormalities to other tumor phenotypes such as ER and PR positive or negative subgroups. The genome-wide scan for LOH in a large set of lobular and ductal cancers will provide the most comprehensive description of allelic loss on lobular cancer to date. Information about morphology-specific traits gained from studying a large number of lobular cancers could lead to an increased understanding of the biology of distinct subsets of breast cancer, provide a basis for studies that would define patient stratification into prognostic and treatment groups and/or inform the development of targeted therapies for specific tumor types.
CA97475	Lampe, Johanna W	2004	Fred Hutchinson Cancer Research Center	Hormone Status Postmenopause: Colonic Bacterial Effects	Breast Cancer Prevention/ Hormone Exposure Endogenous Factors in the Origin and Cause of Cancer Resources and Infrastructure Related to Biology	DESCRIPTION (provided by applicant) Greater exposure to estrogen throughout a woman's lifetime increases her risk of developing breast cancer. In the gut, microflora play a significant role in the metabolism of estrogens. Therefore, inter-individual differences in host bacterial populations may be a determinant of estrogen exposure and ultimately of breast cancer risk. Colonic microfloral production of equol from the soy isoflavone daidzein serves as a biomarker of a unique intestinal bacterial population. Evidence from several studies suggests that, irrespective of soy intake, women with the capacity to produce equol have hormonal profiles associated with a lower risk of breast cancer. Only about one third of individuals have the yet-to-be-identified bacteria capable of producing equol, and equol-producer status can be determined readily from a urine sample collected after a 3-day soy challenge. To date, there has been no systematic study of the effect of equol producer phenotype on estrogen-dependent biomarkers. We propose to examine the association between equol producer phenotype and current and lifetime measures of reproductive hormone exposure. Circulating reproductive hormones and urinary estrogen metabolites will be examined by equol producer phenotype to evaluate current hormonal exposure. Breast and bone densities (markers of lifetime estrogen exposure) will be examined by equol producer phenotype. We will recruit healthy female volunteers, aged 50 to 75 years, from among the 173 women who participated in the Physical Activity and Total Health Study (NCI R01 CA69334; Effect of Exercise on Sex Hormones in Postmenopausal Women). Women in this study had a baseline mammogram to determine percent breast density by computer-assisted technology, total bone density measured by DEXA, a blood sample collected for the analysis of circulating reproductive hormones, and a urine sample collected for the analysis of estrogen metabolites. Thus, by using this study population, we make efficient use of a comprehensive compilation of existing breast density, bone density, and circulating and urinary hormone data. Each woman will complete a 3-day soy challenge and collect the first-void urine on the fourth day for analysis of equol. We will classify women as equol producers or non-producers and will examine differences in percent breast density by equol producer phenotype. In addition, we will establish whether equot production predicts differences in the measures of hormonal exposure, independently of other factors known to be associated with these measures. The results of this study will provide novel data regarding the relationship of the equol-producer phenotype, a marker of colonic nticrofloral environment, to lifetime estrogen exposure.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
CA98741	Campbell-Thompson, Martha	2005	University of Florida	Alternative Estrogen Replacement Therapy for Colon Cancer	Colon and Rectal Cancer Gastrointestinal Tract Complementary and Alternative Prevention Approaches	DESCRIPTION (provided by applicant): Botanical products are becoming increasingly popular as alternatives to estrogen replacement therapy (ERT). Clinical evidence strongly supports an association between ERT and reduced risk of colon cancer in postmenopausal women. After follow-up of women taking combined estrogen-progestin replacement therapy, the Women's Health Initiative recently reported a 37% reduction in colorectal cancer cases compared to women on placebo. In another 20 published studies, half support an inverse association and another quarter shows a significant reduction in risk. Despite these findings, few investigations are underway to determine the mechanisms by which this preventive effect is achieved. Estrogenic effects are mediated by binding to a nuclear receptor and we determined that the second estrogen receptor subtype, ERbeta, is the subtype found in the colonic epithelium. Our studies also showed reduced expression of ERbeta mRNA in colon tumors compared to normal mucosa in female patients. Furthermore, following over-expression of ERbeta, human colon cancer cells displayed reduced proliferation rates and anchorage independent growth. These data imply that ERbeta could mediate the chemoprotective effects for ERT. The overall hypothesis being tested is that alternative ERT based on phytoestrogens with high ERbeta binding activity will reduce colon carcinogensis. Specific aims are proposed to test the following hypotheses: (1) Overexpression of ERbeta in human colon cancer cells will decrease tumorigenic phenotype in vitro (cells in culture) and in vivo (xenograph growth in mice) by interference of EGFR signaling pathways, and (2) A phytoestrogen-enriched diet will reduce experimentally induced aberrant crypt foci by decreasing proliferative activity in the colonic epithelium. The goal of this application is to define how activation of ERbeta-mediated responses can modulate human colon cancer cell growth and whether a red clover extract with ERbeta-selectivity can decrease carcinogen initiated colon tumorigenesis. If phytoestrogens show a chemopreventive effect on colon cancer development and the mechanism is related to ERbeta, these data would clearly expand our understanding of colon cancer and provide a new therapeutic strategy. The ability to pinpoint how an alternative ERT inhibits the adenoma-carcinoma sequence could also lead to more effective methods in preventing cancer recurrence in female patients, as well as developing better chemoprevention strategies in post-menopausal women. The clinical translational potential of this hypothesis lies in the ability of ERbeta positive epithelial cells to respond to phytoestrogens. These results would also suggest additional potential for chemoprevention strategies based on selective estrogen receptor (ERbeta) therapies.
CA99491	Assaf, Annlouise	2003	Memorial Hospital of Rhode Island	The Effect of EtOH and Folate on Hormone Related Cancers	Breast Endometrial Female Genital System Ovarian Exogenous Factors in the Origin and Cause of Cancer	The heavy, regular use of alcohol has been associated with significant morbidity and mortality, particularly in post-menopausal women. The consumption of high levels of alcohol has been associated with increased risk for breast, endometrial, and ovarian cancer. The risks associated with low to moderate alcohol consumption are much less clear. This may be due to differences in hormone replacement therapy or folic acid intake or to the difficulty associated with accurately assessing level of drinking. We hypothesize that high levels of alcohol use will be associated with a higher likelihood of developing breast, endometrial, and ovarian cancer and that folic acid intake will moderate the effect of alcohol on these cancers. Design: The Women's Health Initiative Observational Study cohort consists of 93,717 post-menopausal women who were enrolled between September 1993 until December 1998, nationwide. To date, there have been 1,999 incident cases of breast cancer, 253 cases of endometrial cancer, and 188 cases of ovarian cancer among the women enrolled in this study. Data regarding the use of alcohol, dietary folic acid, and the use of folic acid supplements was collected on each participant at baseline and again at a followup visit. We propose to conduct a secondary data analysis of the effect of alcohol consumption and folic acid intake on the risk of developing these hormone-related cancers. Conclusions: Breast cancer now ranks second in cancer deaths among United States' women and is a leading cause of morbidity. While the incidence of endometrial cancer is not as high, and because of early detection, mortality rates are low, endometrial cancer resulted in over 6,500 deaths in 2001. Ovarian cancer, though much less common, is associated with a very high mortality rate (approximately 50% for all stages) because it is often not detected until late stage. The Women's Health Initiative database provides a unique opportunity to explore the relationship of alcohol and folic acid intake with hormone-related cancers in post-menopausal women.
CP 10128	Brinton, Louise	2003	National Cancer Institute	Breast cancer detection demonstration project follow-up study - I	Breast Ovary Colon Endogenous and Exogenous Factors in the Origin and Cause of Cancer	This study follows about 60,000 women who were former participants in the joint NCI and ACS Breast Cancer Detection Demonstration Project (BCDDP), a nationwide breast cancer screening program conducted during the 1970s. The follow-up started in 1980, with ascertainment of cancer and mortality continuing through 1998. The BCDDP Follow-up Study is particularly valuable for ascertaining the risks and benefits of menopausal hormone replacement therapy associated with cancers of the breast and colon. Analyses are currently under way to examine the relationships between hormone replacement therapy and benign breast disease and to evaluate survival after breast cancer in relation to use of replacement hormones. Research efforts also have focused on mammographic parenchymal patterns and densities in relation to subsequent breast cancer risk and the relation of physical activity, adult diet, alcohol consumption at various ages, and use of certain medications to breast cancer risk. In a recent publication (JAMA 2002; In press) from Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program, women who used estrogen-only replacement therapy, particularly for ten or more years, were found to be at significantly increased risk of ovarian cancer. Women who used short-term estrogen-progestin-only replacement therapy were not at increased risk, but risk associated with short-term and longer-term estrogen-progestin replacement therapy warrants further investigation.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
NR05084	Avis, Nancy	2006	Wake Forest University Health Sciences	Acupuncture Treatment for Menopausal Hot Flashes	Breast Complementary and Alternative Treatment Approaches Patient Care and Survivorship Issues	DESCRIPTION (provided by applicant) Hot flashes and/or night sweats are the most common and troubling symptoms associated with menopause. For many women these symptoms can be frequent and severe enough to become debilitating and interfere with daily activity. They often occur at night, waking women from sleep and leading to daytime irritability, fatigue and depressed mood. Relief from hot flashes and night sweats has been shown to be the primary reason that women initiate hormone therapy (HT). Hot flashes are a particular problem for women who have had treatment for breast cancer. Currently, the gold standard for treatment of vasomotor symptoms is estrogen therapy. HT, however, is associated with a number of risks and is often contraindicated for women at high risk for breast cancer and those who have had breast cancer. Given the risks and side effects associated with HT, many women have sought alternative treatments for hot flashes. Unfortunately, many of these treatments have a high incidence of side effects or have not been shown to be effective. Modern theories of neurophysiologic and neurohumoral mechanisms, as well as concepts of Traditional Chinese Medicine (TCM) suggest that acupuncture may be an effective method to control menopausal hot flashes. A few small pilot studies, as well as clinical practice, have provided some support for acupuncture as an effective treatment. The goal of this R21 pilot grant is to demonstrate the feasibility of conducting a randomized clinical trial to test the effectiveness of acupuncture for treating menopause-related hot flashes. Following this pilot grant, we plan to seek R01 funding to conduct a fully powered randomized trial. For this pilot grant, 60 women will be randomly assigned to one of 3 groups: (1) standardized acupuncture with variation, (2) placebo "sham" acupuncture, or (3) usual care. Our primary outcome will be a reduction in hot flash frequency and severity. Secondary outcomes will include improvement in sleep, mood, and overall quality of life. The purpose of this pilot study is to establish the acupuncture treatment and the placebo acupuncture protocols and to demonstrate the feasibility of recruiting and retaining subjects to the study. The study is organized with Wake Forest University School of Medicine (WFUSM) serving as the Coordinating Center and Massachusetts General Hospital (MGH) and the University of North Carolina at Chapel Hill (UNC) serving as the clinical sites. The specific aims of this pilot grant are: (1) to develop and refine the acupuncture protocols, (2) to determine the feasibility of conducting the proposed R01 in terms of recruiting subjects to the study and retaining subjects throughout the study, (3) to obtain preliminary data on the effectiveness of acupuncture on hot flash frequency and severity, as well as to obtain data on these outcomes to determine sample size calculations for the R01, and (4) to assess our ability to track program costs associated with the intervention and to identify costs borne by participants.
CA104852	Zeleniuch-Jacquotte, Anne	2008	New York University School of Medicine	Endogenous Estrogens and Colorectal Cancer Risk in Women	Colon and Rectal Cancer Gastrointestinal Tract Endogenous Factors in the Origin and Cause of Cancer	DESCRIPTION (provided by applicant): The evidence from epidemiologic studies that hormone replacement therapy is associated with a decreased risk of colorectal cancer (CRC) has been considerably strengthened by the recent observation of a statistically significant reduction in risk of CRC in the Women's Health Initiative, a large, randomized, placebo-controlled, clinical trial. Despite the evidence on the protective role of exogenous estrogens in CRC development, there are no epidemiologic studies to date on the association of endogenous estrogens with CRC risk. We propose to test the hypothesis that postmenopausal serum levels of estrogens and androgens are negatively associated with subsequent risk of CRC in a case-control study nested within the New York University Women's Health Study (NYUWHS) cohort. Between 1985 and 1991, the NYUWHS enrolled 14,275 healthy women who have been actively followed up ever since. Serum samples collected at time of enrollment were frozen for future biochemical analyses. A total of 227 cases of colorectal adenocarcinoma are expected to be diagnosed by March 2005 in participants who were postmenopausal at entry, and these cases will be included in the proposed study. For each case, two controls will be selected who match the case on age at, and date of, enrollment, and menopausal status at enrollment. Frozen serum samples from cases and matched controls will be retrieved and assayed for estradiol, estrone, estrone sulfate, androstenedione, testosterone, and SHBG. Data on potential confounders were collected previously. This study will be the first study on the association of postmenopausal circulating estrogen and androgen levels with CRC risk. The NYUWHS is particularly well suited to study the proposed hypothesis because of its prospective design which minimizes the risk for bias and allows to examine pre-diagnostic hormone levels, and because the role of endogenous sex hormones in the development of diseases has always been its primary focus.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
CA110797	Modugno, Francesmary	2006	University of Pittsburgh	The Role of Prolactin in Postmenopausal Breast Cancer	Breast Endogenous Factors in the Origin and Cause of Cancer	DESCRIPTION (provided by applicant): Laboratory data suggests that prolactin (PRL), a hormone that controls breast development and lactation, may also play a role in breast carcinogenesis. Data in humans has been sparse consisting of mainly case-control studies with extremely small sample sizes. Only one large prospective study (the Nurses" Health Study) has examined the question, noting a significant positive association between plasma PRL levels similar in magnitude to that of estrogen and breast cancer. If validated, these findings would suggest additional areas for focused research into the development of chemopreventive agents, similar to the development of SERMS for breast cancer prevention. Thus, a large prospective study is urgently needed. The objective of this application is to prospectively evaluate the extent to which PRL levels are related to breast cancer in postmenopausal women. We will specifically test the following hypothesis: Among postmenopausal women, serum prolactin levels are positively associated with breast cancer risk. We will further evaluate the effects of sex steroid hormones and growth factors levels on the prolactin-breast cancer association. As a secondary aim, we will explore the relationship of prolactin levels to clinical characteristics of breast cancer, including tumor stage, grade and ER/PR status. We will undertake a case-cohort study within the Study of Osteoporotic Fractures (SOF). SOF is a prospective study that collected risk factor data and banked fasting serum on 9704 postmenopausal women in the United States. Since 1986, 481 women were diagnosed with breast cancer after enrollment. We will measure prolactin levels in the prospectively-collected serum of 375 women who developed breast cancer during follow-up and 375 SOF participants who did not develop the disease during follow-up. To assess the relationship between prolactin and breast cancer, we will use Cox regression models controlling for covariates such as age, family history, age at first birth, age at menarche, age at menopause, past use of hormone replacement therapy, parity, ever breast fed, and history of benign breast disease, as well as factors affecting prolactin. A positive finding in our study will support the development of breast cancer chemopreventive agents aimed at the prolactin pathway. Approval for this study has already been obtained from SOF and we can begin the study as soon as funding is obtained.
CA113023	Dorgan, Joanne	2005	Fox Chase Cancer Center	Pilot Study of Adrenal Hormones	Breast Exogenous Factors in the Origin and Cause of Cancer	DESCRIPTION (provided by applicant): Breast Cancer is a hormonally dependent cancer, and it has recently been shown that postmenopausal women with elevated serum levels of androgens as well as estrogens are at an increased risk of developing breast cancer. Of particular interest, postmenopausal women with high levels of the adrenal androgens, dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), are approximately twice as likely to develop breast cancer compared to those with lower levels. In the proposed pilot study, we will obtain preliminary data requested by reviewers for a revised R01 application to prospectively determine if increased enzymatic activity at specific step(s) in the steroidogenesis pathway is responsible for increased adrenal androgens in postmenopausal women who develop breast cancer. Specific aims for the proposed pilot study are: 1) quantify the reproducibility of laboratory assays to measure serum pregnenolone, 17OH-pregnenolone, progesterone, 17OH-progesterone, cortisol, and 11-deoxycortisol; and 2) determine if a single measurement of pregnenolone, 17OH-pregnenolone, progesterone, 17OH-progesterone, cortisol, and 11-deoxycortisol adequately reflects longer-term levels. For aim 1, serum aliquots from the same blood draw from 4 women who donate blood to the Fox Chase Biosample Repository will be measured multiple times in multiple assay batches. Coefficients of variation and intraclass correlation coefficients will be calculated to evaluate assay reproducibility. For aim 2, hormones will be measured in serum collected at two different times from 20 women who donated serum to the Columbia, MO Serum Bank. Intraclass correlation coefficients will be calculated to evaluate whether hormone measurements in a single aliquot reflect longer term levels.

National

Eye

Institute

(NEI)

National Eye Institute
FY 2004 Menopause Related Research

The National Eye Institute (NEI) supports menopause related research in the following areas:

- Dry eye: Lacrimal insufficiencies affect roughly two million Americans, particularly post-menopausal women. NEI-supported researchers are investigating the hypothesis that lacrimal insufficiency is triggered by loss of hormonal support for the lacrimal gland's secretory capacity. Much of the dry eye disease that afflicts women after menopause
- The role of estrogen in the etiology of glaucoma and cataract
- Antioxidant effects of estrogen in age-related macular degeneration:

Grant:	5R01EY011239-08	
Program Director:	FISHER, RICHARD S	
Principal Investigator:	AGRE, PETER C	MD INTERNAL MED
Title:	Aquarporin Water Channel Proteins in Eye	
Institution:	JOHNS HOPKINS UNIVERSITY	BALTIMORE, MD
Project Period:	1996/02/01-2006/06/30	

DESCRIPTION: (provided by applicant): Numerous physiological and pathophysiological processes involve the transport of water across cell membranes. The molecular identity of water transporters became known with discovery of the aquaporin family of membrane water channels. Four of the ten known mammalian aquaporins are expressed in anterior segment of eye. This application addresses the molecular mechanisms regulating function of human AQPO, AQP1, AQP3, and AQP5 and dysfunction of these proteins in clinical disorders of eye. Aim I. Analysis of aquaporin proteins in normal human eye. New reagents will be prepared including plasmids encoding wild-type, site-directed mutant, and epitope-tagged human AQPO, AQP1, AQP3, and AQP5. Antibodies specific for the N- and C-termini of the human proteins will be raised in rabbits and affinity-purified. The biophysical functions of human aquaporins will be expressed in Xenopus laevis oocytes and analyzed at baseline and after activation. Human aquaporins will be expressed in yeast and purified for reconstitution into proteoliposomes for permeation studies, into planar bilayers for analysis of electrophysiological properties, and into membrane crystals for structural studies. The distribution of these aquaporins will be defined in normal human eye. Aim II. Analysis of aquaporin proteins in clinical disorders of eye. The distribution of human aquaporins will be defined in tissues from patients with cataract or Sjogren's syndrome. Basic mechanisms by which AQPO and AQP5 may contribute to these disorders will be sought including defects in water and solute permeation, membrane trafficking, subunit oligomerization, and internalization, Physiological deficits will also be evaluated in rodent models of AQPO degradation and AQP5 deficiency.

Grant:	5R01EY014847-02	
Program Director:	FISHER, RICHARD S	
Principal Investigator:	ARGUESO, PABLO	PHD
Title:	O-Glycans on Mucins at the Ocular Surface	
Institution:	SCHEPENS EYE RESEARCH INSTITUTE	BOSTON, MA
Project Period:	2003/09/01-2008/08/31	

DESCRIPTION (provided by applicant): Mucins are a family of large and heavily O-glycosylated glycoproteins synthesized by all wet-surfaced epithelia, including the corneal and conjunctival epithelia. The ocular surface epithelia produce the secreted mucin MUC5AC and the membrane-associated mucins MUC's 1, 4 and 16. Terminal carbohydrates on mucins are the most exposed to the extracellular milieu, but little is known about their roles and character in each mucin at the ocular surface. Our previous studies have demonstrated that binding of an antibody specific to a terminal carbohydrate on MUC16 is altered in dry eye patients. This proposal is aimed at identifying terminal carbohydrate structures on individual ocular mucins, the enzymes involved in their biosynthesis and the role of terminal O-glycans in maintaining a wet ocular surface and preventing pathogen invasion. AIM I: We hypothesize that individual mucins are differentially O-glycosylated by the ocular surface epithelia. We propose to: A. Characterize the repertoire of terminal O-linked carbohydrates on individual mucins isolated from tears of normal individuals. B. Identify and localize glycosyltransferases (sialyltransferases) responsible for their biosynthesis. C. Test in vitro the role of terminal O-linked carbohydrates on mucins of the glycocalyx in conferring disadhesive properties to epithelial cells and resistance to transfection with adeno-associated viruses. AIM II: We hypothesize that in dry eye patients there is an alteration in terminal O-glycan structures of the membrane-associated mucins that affects hydration of the ocular surface. We propose to: A. Determine if there is an alteration of terminal carbohydrates of each membrane-associated mucin purified from the apical tear surface of dry eye patients. B. Determine if there is an alteration in the expression of glycosyltransferases (sialyltransferases) in dry eye patients. C. Determine in vitro whether the depletion of terminal carbohydrates on mucins in corneal and conjunctival cells enhances the penetrance of rose bengal into these cells. AIM III: We hypothesize that O-linked carbohydrates present on the secreted mucin MUC5AC in the tear fluid have specific affinity to P. aeruginosa, preventing their attachment to the ocular surface glycocalyx and facilitating their clearance. We propose to: A. Compare the binding of P. aeruginosa to the O-linked carbohydrates of individual mucins collected from tears. B. Determine in vitro how inhibition of O-glycan synthesis on membrane-associated mucins affects P. aeruginosa adherence to corneal cells.

Grant:	1R41EY015991-01	
Program Director:	HELMSEN, RALPH J	
Principal Investigator:	BENNETT, GREGORY	MD
Title:	Nanoliter Tear Osmometer for the Detection of Dry Eye	

Institution: OPTICOLOGY, INC. NEW YORK, NY

Project Period: 2004/09/30-2005/03/31

This research intends to develop a Nanoliter Tear Osmometer for the detection of the presence and degree of dry eye. It is estimated that 40-60 million Americans have dry eye symptoms. Prescription pharmaceuticals are appearing on the market to treat dry eye yet methods for diagnosis and monitoring treatment remain problematic. This Phase I research will make use of a new technology for analyzing tear osmolarity, which is popularly accepted by experts in the field as an indicator of the occurrence and severity of dry eye. Specifically, the research will develop an instrument to analyze nanoliter volumes of tears that offers quick, reliable, and an accurate measure of osmolarity. It is the intention of research team to develop a system that is simple to use and requires no special training thereby making it a suitable device for the clinical ophthalmologist or optometrist. The technological approach proposed is unique and innovative, as it overcomes many of the shortcomings of conventional osmolarity measurements. Commercial potential for such a device is high, since it is projected that cost in production will be in-line with other instruments purchased by clinicians. The pharmaceutical industry has invested large dollar amounts into treatment of dry eye and expect large returns in the next several years. With this introduciton of prescription treatment of dry eye it may become a necessity to have proper a diagnostic tool, and the osmometer proposed has attributes ideally suited for clinical examinations. The use of existing proven technology and applying it to tear osmolarity forms the basis of this Phase I research. Several factors on the effectiveness of measuring tear osmolarity will be examined, including resolution, sensitivity, and overall performance. The research will conclude with an IRB approved study.

Grant: 1R01EY015304-01

Program Director: LIBERMAN, ELLEN S

Principal Investigator: BERNSTEIN, STEVEN L MD OPHTHALMOLOGY

Title: A functional approach to treating optic nerve stroke

Institution: UNIVERSITY OF MARYLAND BALT PROF SCHOOL
BALTIMORE, MD

Project Period: 2004/08/01-2007/05/31

DESCRIPTION (provided by applicant): Isolated axonal strokes comprise more than 3/4ths of the 166,000 strokes that occur in the US every year, but until now there has been no in-vivo model to analyze this stroke form. We have developed a new rodent anterior ischemic optic neuropathy (rAION) model of CNS axonal stroke that directly correlates with human AION. We have characterized the response of the neurons and optic nerve following axonal stroke. We have determined that rAlON results in optic nerve demyelination and loss of function. We have also found that estrogen significantly reduces the loss of neurons following rAION. We hypothesize that: 1) axon ischemia-associated demyelination blocks optic nerve repair. 2) Estrogen enhances post-stroke optic nerve recovery. Our proposal is designed to answer three related questions: 1) What RGC axonal transport and glial changes occur in-vivo following rAION, contributing to permanent optic nerve damage? To answer this question, we will use the rAION model to define early retina and optic nerve stress-related cellular events, and identify the time course of optic

nerve demyelination and remodeling resulting from optic nerve stroke. This work will be performed using histological, electrophysiological, and molecular methods. 2) Can reducing post-stroke demyelination increase post-stroke function? With the rAION model, we will use anti-demyelinating drugs, to determine whether reducing post-stroke demyelination decreases permanent optic nerve damage and increases function. This work will be performed using electrophysiological, stereotactic retrograde tracing, molecular, and histological methods. 3) Does estrogen also exert neuroprotective effects when administered after optic nerve insult? With the rAION model, estrogen and estrogen inhibitors, electrophysiological, histological, stereotactic, and molecular methods, we will determine the effect of differences in dose, timing, sex, and blockade of endogenous estrogen. Our experimental results obtained with this model will enable rational design of clinically effective, neuroprotective strategies that can minimize ischemic axonal stroke damage.

Grant:	1R01EY015857-01
Program Director:	FISHER, RICHARD S
Principal Investigator:	CANDIA, OSCAR A
Title:	Fluid Movement across Conjunctiva: Stimulation and Reg.
Institution:	MOUNT SINAI SCHOOL OF MEDICINE OF NYU NEW YORK, NY
Project Period:	2004/09/01-2008/08/31

DESCRIPTION (provided by applicant): We have previously characterized the isolated rabbit conjunctiva as an epithelial model of Na absorption and CI secretion. Our hypothesis was that these transport mechanisms, by providing the driving forces for fluid movement across the tissue, could enable the conjunctiva to either absorb fluid from, or contribute fluid to, the aqueous layer of the tear film. This was demonstrated with direct experiments using the rabbit epithelium. Our current hypothesis is that the human conjunctiva may also possess transporters that enable it to absorb Na and secrete CI with the consequent fluid absorption or secretion. For this fluid flow to occur, the conjunctiva must have (as most fluid transporting epithelia do) water channels, which are usually different in the apical and basolateral domains. We thus propose to identify with biochemical and histochemical protocols, the electrolyte transporters and water channels (aquaporins) in the human conjunctiva relevant towards the movement of fluid flow across the epithelium. Because receptor-mediated responses are atypical in rabbit conjunctiva, assays similar to those in human will be done on murine and porcine tissues to determine the best model for fluid transport in the human conjunctiva. Since aquaporins (AQPs) play a crucial role in fluid transport, and our experiments have shown that anisotonic conditions and cAMP-elevating agents can modify water permeability, protocols to understand the regulation of water permeability in murine and porcine tissues will be implemented. Biochemical, histochemical and functional experiments will be conducted on mice, rat and pig conjunctivae. From the determination of the transporters, the AQPs, and the functional physiological experiments that can be done on the conjunctiva of the selected animal models, a theoretical model for the fluid movement across the human conjunctiva will be proposed. From these studies we expect to expand the understanding of the physiology of the mammalian conjunctival epithelium, and provide evidence that direct or receptor-mediated stimulation of ionic transport mechanisms will result in fluid secretion towards the tear film. These studies may provide the groundwork for the design of future treatment modalities for dry-eye syndromes.

Grant:	5U10EY013626-03
Program Director:	KURINIJ, NATALIE
Principal Investigator:	COLEMAN, ANNE L MD
Title:	Incidence of late macular degeneration in older women
Institution:	UNIV. OF CALIFORNIA LOS ANGELES LOS ANGELES, CA
Project Period:	2002/08/15-2007/07/31

DESCRIPTION: (Applicant's Abstract) Age-related macular degeneration is the number one cause of irreversible blindness in the United States and is more prevalent in older, Caucasian women. Although there have been several studies on the incidence of ARM, none of these studies has been able to provide accurate estimates on the incidence of late ARM and/or the progression of ARM in the oldest old, those individuals over 80 years of age, because of the limited sample sizes in these studies in this age group. The population in the Study of Osteoporotic Fractures (SOF) is an appropriate cohort in which to evaluate the incidence of late ARM and the progression of ARM, because the mean age of the women at the re-examination will be 84.4 years of age and the sample is mainly Caucasian. The proposed research study aims to determine the incidence of late ARM, the rate of progression of ARM, and the association of specific risk factors such as diabetes mellitus and prior cataract surgery with late ARM and the progression of ARM in elderly women. In addition, it aims to determine the trajectory of visual decline in older women over a 14- year period. Secondarily, it aims to determine the impact of late ARM on vision-targeted health-related quality of life and to determine whether or not an association exists between the progression of ARM and the risk of falling and hip/non-spine fractures. In 1997 to 1998 (Visit 6), 5482 women had an eye examination that consisted of a medical and ocular history, nine questions from the National Eye Institute Visual Function Questionnaire (NEI-VFQ), and measurements of visual acuity, contrast sensitivity, peripheral vision with automated perimetry, intraocular pressure, and uncorrected refractive error. These women also had a refraction and imaging of their lenses and fundi of both eyes through dilated pupils. Approximately 4.5% of these women have photographically validated late ARM, 41.5% have early ARM, and 54% have no ARM or hard drusen only. In the proposed re-examination, we will update their medical and ocular history and ask them the nine questions from the NEIVFQ. In addition, visual acuity and contrast sensitivity will be re-measured. Fundus photographs of both eyes through dilated pupils will be obtained. These photographs and the relevant photographs from 1997 to 1998 will be graded for ARM with the Wisconsin Age-Related Maculopathy Grading System (WARMGS) in a masked fashion so that the readers do not know which film is from which visit. The University of Wisconsin will also grade the fundus photographs on 30% of the eyes with ARM and 10% of the total sample. This will allow the identification of women in SOF who have had progression of their ARM and developed late ARM since 1997 and 1998.

Grant:	2R01EY012245-05
Program Director:	HUNTER, CHYREN
Principal Investigator:	CORTOPASSI, GINO A
Title:	Mitochondrial Mechanisms in Optic Neuropathy
Institution:	UNIVERSITY OF CALIFORNIA DAVIS DAVIS, CA

Project Period: 2000/05/01-2009/04/30

DESCRIPTION (provided by applicant): Our long-term objective is to clarify the mitochondrial pathogenetic mechanisms of both Leber's Hereditary Optic Neuropathy (LHON) and Dominant Optic Atrophy (DOA), which eventually causes optic neurodegeneration as a result of two distinct mitochondrial causes, defects in which may be integrated into a common pathophysiological pathway. Our microarray analyses have supported an alternative mechanism for LHON, and thus our Aims have been focused in that direction. Firstly, we propose to confirm the altered expression of 'gene leads'by RT-PCR and Western and Elisa, and to assay the effects of LHON mutations on secretion and cell migration in LHON and DOA cell models. Secondly we will test alterations in Complex 1, and of mitochondrial structure. Thirdly, we will dissect the source of altered mitochondrial Ca 2+ signaling in LHON models. Fourthly, we will attempt to create new cellular LHON models to strongly test the hypotheses, and to test possible homologies between LHON and DOA by microarray. Lastly, we will begin to test mechanism-based compounds, and to also begin random screening of compounds, for anti-LHON and anti-DOA effects.

Date Run: 03/16/05 **PUBLIC ABSTRACTS**

Grant: 5R01EY006177-20

Program Director: FISHER, RICHARD S

Principal Investigator: DARTT, DARLENE A PHD

Title: Mechanism of Lacrimal Gland Secretion

Institution: SCHEPENS EYE RESEARCH INSTITUTE BOSTON, MA

Project Period: 1985/06/01-2006/05/31

DESCRIPTION (provided by applicant): A decrease in secretion or an alteration in the composition of lacrimal gland fluid is a primary cause of the ocular surface problems that occur in aqueous tear-deficient dry eye resulting from lacrimal gland disease, contact lens wear, LASIK surgery, and aging. Parasympathetic and sympathetic nerves are well-known stimuli of lacrimal gland secretion and the signaling pathways activated by these stimuli have been characterized. A new type of stimulus of lacrimal gland secretion, epidermal growth factor (EGF), has been identified. Based on this finding, the following working model has been proposed for the present grant: Activation of sensory nerves from the ocular surface stimulates parasymapthetic and sympathetic nerves that innervate the lacrimal gland to release their neurotransmitters. These neurotransmitters activate specific signaling pathways to stimulate the synthesis of EGF and cause its release by ectodomain shedding from the basolateral membranes. The released EGF interacts with EGF (erbB) receptors on the lacrimal gland acinar cells activating a signaling pathway that causes secretion of proteins including the shedding of EGF family members from the apical membranes. These growth factors are released into lacrimal gland fluid to protect the ocular surface. The long term goal of the experiments described in this proposal is to test this model. From the results of the proposed study, new treatments for dry eye, based on stimulating EGF-, cholinergic, and alpha1-adrenergic-dependent signaling pathways to induce secretion, could be developed. To reach this goal the following specific aims have been proposed: 1) Which EGF receptor subtypes participate in stimulation of lacrimal gland secretion?; 2) Which cellular signaling pathways does EGF activate to stimulate lacrimal gland protein secretion?; and 3) How are the expression and release of EGF, transforming growth factor (TGF) alpha, and other EGF family members regulated? Acini will be prepared from rat lacrimal glands. Immunoprecipitation, Western blot analysis, immunofluorescence microscopy, and EGF receptor deficient mice will be used to determine if EGF activates and alpha1-adrenergic agonists transactivate

EGF receptors to stimulate secretion. Biochemical assays, inhibitors, and adenovirus transduction will be used to determine the cellular signaling pathways activated by EGF compared to cholinergic and alpha1-adrenergic agonists. lmmunofluorescence microscopy, Western and Northern blot analysis, and RT-PCR will be used to determine how the expression and release of EGF and its family members is regulated.

Grant: 3R03EY014627-01S1

Program Director: LIBERMAN, ELLEN S

Principal Investigator: DYNLACHT, JOSEPH R PHD

Title: Effect of Estrogen on Radiation-induced Cataractogenesis

Institution: INDIANA UNIV-PURDUE UNIV AT INDIANAPOLIS
INDIANAPOLIS, IN

Project Period: 2003/09/30-2006/08/31

Abstract Text Not Available

Grant: 5R03EY014627-02

Program Director: LIBERMAN, ELLEN S

Principal Investigator: DYNLACHT, JOSEPH R PHD

Title: Effect of Estrogen on Radiation-induced Cataractogenesis

Institution: INDIANA UNIV-PURDUE UNIV AT INDIANAPOLIS
INDIANAPOLIS, IN

Project Period: 2003/09/30-2006/08/31

DESCRIPTION (provided by applicant): The induction of cataracts is often an unfortunate and unavoidable consequence of conventional radiation therapy for head and neck or ocular tumors, whole-brain irradiation, and total-body irradiation prior to autologous bone marrow transplantation. Though not life-threatening, radiation-induced cataractogenesis represents a potentially serious sequelae of radiotherapy which can require surgical intervention. While the cellular and molecular mechanism(s) of radiation-induced cataractogenesis have not been clearly elucidated, damage to the genome at the time of exposure and subsequent proliferation of the radiosensitive cells in the germinative zone of the lens epithelium likely play a role in the process. Using a rat model, we have recently accumulated preliminary data which indicate that estrogen reduces the latent period and may increase the incidence and severity of radiation-induced cataracts. High estrogen levels are artificially induced in nonpregnant women using oral contraceptives, or in post-menopausal women on estrogen replacement therapy, and these groups may be at an increased risk for developing cataracts which are more severe or occur with a more rapid onset. Estrogens regulate several proteins involved in cell cycle control and apoptosis, and its metabolism results in the production of free radicals which may be genotoxic and mutagenic to mammalian cells. Thus, a novel hypothesis to be tested in the proposed studies is that estrogen alters cell cycle regulation, DNA double strand break induction or repair, and proliferation in irradiated lens cells. We shall also

investigate the dose-time interactions of radiation and estradiol to better understand the mechanism of estrogen action, and we will determine whether estrogen-modulation of radiation cataractogenesis is estrogen receptor (ER)-mediated using knockout mice that are deficient in either ERalpha or ERbeta. The lens has frequently been used as a model for predicting delayed (late) effects in other irradiated tissues. Data obtained from the proposed study may demonstrate that the lens is a useful model for predicting late effects in other estrogen-responsive target tissues. Finally, the efficacy of utilizing a novel technique for small animal irradiations shall also be tested; in this study, using the Leksell Gamma Knife, only one eye shall be irradiated in each of the animals, with the contralateral eye serving as a control.

Grant:	5R01EY014594-02	
Program Director:	LIBERMAN, ELLEN S	
Principal Investigator:	EISNER, ALVIN	PHD
Title:	Female Hormones and Vision	
Institution:	OREGON HEALTH & SCIENCE UNIVERSITY	PORTLAND, OR
Project Period:	2003/04/01-2007/02/28	

DESCRIPTION (provided by applicant): The long-term goal is to elucidate the roles that female hormones have on the eye and vision. The information gained is expected to provide quantitative means of assessing duration-dependent effects of medications that affect estrogen receptors or that alter estrogen levels. The clinical emphasis will be on 2 types of medications - selective estrogen receptor modulators (SERMS) and aromatase inhibitors. Both are used as adjuvant therapy for early-stage breast cancer, or are likely to be used for this purpose or for breast cancer prophylaxis. SERMS can act either as estrogen agonists or antagonists depending on the target tissue. Aromatase inhibitors block the production of estrogen. The main objective is to identify the functional and anatomical changes that occur in the eye and visual system as a result of estrogen-receptor action and to elucidate the effects of 2 SERMS, tamoxifen and raloxifene, as functions of their durations of use. Because tamoxifen has long been the medication of choice for adjuvant breast cancer therapy and has been shown to affect the eye and vision, it will serve as the focus. In this way, potential side effects of newer medications can be compared against those of the standard of care. The main use of raloxifene at present is to prevent osteoporosis. The aromatase inhibitor to be evaluated, anastrozole, currently is used for treating advanced breast cancer. There are 4 specific aims: (1) To define the changes of visual function that occur during the 5-year period of tamoxifen use. A longitudinal design will be used to test 2 hypotheses: a) that tamoxifen alters the adaptation properties of SWS-cone pathways in the visual-field periphery, and b) that 2 distinct tamoxifen-user response groups can be defined on the basis of visual changes that occur after several years. Psychophysical measures will be compared with results of automated perimetry. (2) To determine the time course of tamoxifen-induced changes of ocular anatomy. A longitudinal design will be used to test the hypothesis that the retinal nerve fiber layer often thickens during year 1 of tamoxifen use but later thins. Anatomical measures will be made using the Heidelberg Retina Tomograph and the Zeiss Ocular Coherence Tomograher. (3) To distinguish the effects of raloxifene and anastrozole from those of tamoxifen. The same techniques will be used as for Specific Aims 1 and 2. (4) To determine the prevalence of cyclic changes of SWS-cone-mediated sensitivity across the menstrual cycle. Data from healthy women who are identified as having large cyclic sensitivity changes will be obtained from high and low estrogen-response portions of the menstrual cycle, and the visual changes that occur over weeks will be used to help interpret effects of prolonged exposure to SERMS.

Grant: 5R01EY014477-02

Program Director: MARIANI, ANDREW P

Principal Investigator: ELLIOT, SHARON J PHD

Title: ECM Regulation by Estrogen in ARMD

Institution: UNIVERSITY OF MIAMI-MEDICAL CORAL GABLES, FL

Project Period: 2003/07/01-2007/06/30

DESCRIPTION (provided by applicant): Age-related macular degeneration (ARMD) is the most important cause of lost central vision in the elderly. Although ARMD pathogenesis is unknown, oxidant injury to the RPE has been implicated as a mechanism. Since oxidant-mediated cellular injury leads to dysregulation of extracellular matrix (ECM) turnover by injured cells in many age-related degenerative disorders, this may also be the case for injured RPE. Additionally, dysregulated MMP-2 and its major substrate type IV collagen, may be induced in injured RPE to promote ARMD progression by macrophage-derived oxidants, myeloperoxidase (MPO), as well as macrophage-derived cytokines, especially tumor necrosis factor-alpha (TNF-alpha). Alternatively, estrogens, which are natural antioxidants and modulators of the molecules involved in ECM turnover, might oppose the injurious effects of macrophage-derived oxidants and cytokines on RPE production of MMP-2 or collagen. Based on preliminary data, we postulate that macrophage-derived MPO injures the RPE cell membrane to induce bleb formation but with simultaneous down-regulation of MMP-2 (leading to trapping of the blebs as subRPE BLD). Subsequent RPE exposure to macrophage-derived TNF-alpha, during a vulnerable post-blebbing period, will stimulate increased MMP-2 and collagen expression. Conversely, we expect that estrogen's antioxidant action on the cell membrane will diminish MPO-induced blebbing and that activation of estrogen receptors will modify matrix molecule dysregulation.

Grant: 5R01EY003306-26

Program Director: FISHER, RICHARD S

Principal Investigator: GIPSON, ILENE K.

Title: MUCINS OF THE OCULAR SURFACE

Institution: SCHEPENS EYE RESEARCH INSTITUTE BOSTON, MA

Project Period: 1979/08/01-2005/07/31

The mucus of the tear film is responsible for maintenance of fluid on the surface of the eye and for providing a microbe barrier to protect the eye from infection. Ocular surface diseases such as those of the dry eye type, vitamin A deficiency, ocular surface infections as well as allergic conjunctivits may involve mucus deficiency, disruption of the mucus layer, or discharge of large amounts of mucus. During the previous funding period, we demonstrated that three mucin genes are expressed by the ocular surface epithelium, two prevalent ones being the membrane- spanning mucin MUC4 and the goblet cell-specific mucin MUC5AC. We sequenced portions of MUC4 and developed probes, antibodies, and assay methods for both mucins that we now propose to use in four specific aims toward understanding aspects of the

function and regulation of expression of these mucins on the ocular surface in normal and pathologic states. Aim I: Characterize two aspects of the membrane-spanning mucin MUC4 on the ocular surface. A. determine whether the mucin remains associated with the apical membrane glycocalyx or whether its extracellular domain is shed into the tear film. b. Test candidate inducers of MUC4 gene expression, based on presence of putative transcription factor binding sites identified from sequencing the MUC4 regulatory region and on preliminary data indicating their potential role in its regulation. Aim II: We hypothesize that conjunctival goblet cell differentiation is characterized by induction of expression of the MUC5AC gene and that such induction can be regulated by environmental stimuli as well as cellular effectors. We propose to: a. determine in a mouse model whether goblet cell differentiation/Muc5AC expression can be influenced by surface irritants, infections, or specific allergens; b. determine whether conjunctival goblet cell differentiation can be enhanced in vitro, based on demonstrated presence of regulatory elements in the promoter region of MUC5AC and on culture conditions known to affect gastrointestinal goblet cell differentiation. Aim III: Determine if MUC5AC has specific affinities for MUC4 and the bactericidal proteins prevalent in the tear film, lysozyme, and secretory IgA. Aim IV: Determine in a specific type of dry eye (Sjogren's syndrome), and in seasonal allergic conjunctivitis whether amounts of MUC4 and MUC5AC mRNA and protein differ from the normal population. We hypothesize that dry eye syndromes are characterized by loss of surface wetting due to reduced amounts of MUC5AC and MUC4 protein, whereas, allergic conjunctivitis is characterized by an increased amount of mucins to facilitate allergen removal.

Grant:	5R01EY011224-09	
Program Director:	FISHER, RICHARD S	
Principal Investigator:	GLASGOW, BEN J	MD
Title:	PROTEINS IN MOLECULAR MECHANISMS OF TEAR FILM FORMATION	
Institution:	UNIV. OF CALIFORNIA LOS ANGELES	LOS ANGELES, CA
Project Period:	1996/02/01-2006/01/31	

DESCRIPTION (Adapted from applicant's abstract): The tear film is composed of a complex mixture of protein, lipid and mucin components that lubricate and protect the human ocular surface. The long term objective of this application is to understand better the molecular mechanisms of the protein components in human tears. This application focuses on the structure-function relationships of tear lipocalin (TL), the principal lipid binding protein in tears. The knowledge of the requirements and mechanisms of the normal components of the tear film will be useful in achieving the ultimate goal of treating dry eye diseases. The experimental approach takes advantage of a combination of recent methods for monitoring lipid binding and elucidating protein structure including electron paramagnetic resonance (EPR), site directed spin labeling, and site-directed tryptophan fluorescence (SDTF). SDTF was recently developed in this laboratory and involves the sequential replacement of amino acids with tryptophan to provide information about solution structure and backbone motion of proteins with a real-time resolution in the nanosecond range. This application is designed to capitalize on and advance this technology in accomplishing the following Specific Aims: 1) To test the hypothesis that tear lipocalin scavenges and solubilizes lipids from the corneal surface; 2) To investigate the molecular mechanisms of lipid binding in tear lipocalin. The hypothesis that tryptophan 17 and isoleucine 98 contribute to strand interactions to form a hydrophobic cluster for lipid binding will be tested. 3) To determine the secondary structure of the D, E,

and F strands of tear lipocalin in solution; 4) To determine structural configurations that confer ligand specificity. The hypothesis that the loop between the E and F strands acts as a pH dependent gate for ligand access to the lipid binding core of tear lipocalin will be tested. In order to design logical treatment strategies including pharmacological solutions for dry eye disease, it is imperative to understand the molecular mechanisms involved in the normal function of tear film components. This project is anticipated to contribute to this understanding.

Grant:	2R01EY011386-08	
Program Director:	FISHER, RICHARD S	
Principal Investigator:	HAMM-ALVAREZ, SARAH F	PHD
Title:	Microtubule-based transport in lacrimal gland function	
Institution:	UNIV. OF SOUTHERN CALIFORNIA	LOS ANGELES, CA
Project Period:	1996/07/01-2009/03/31	

DESCRIPTION (provided by applicant): A major contribution to ocular morbidity is lacrimal dysfunction, affecting over 10 million Americans, primarily women. At least two to four million cases are autoimmune-mediated and accompanied by additional symptoms, which lead to the diagnosis of Sjogren's syndrome. Development of primary lacrimal deficiency and Sjogren's syndrome are associated with changes in hormonal status and also environmental and genetic factors. Although the precise mechanisms involved in disease development remain unclear, these diseases are associated with impaired release of secretory products into ocular surface fluid by the lacrimal gland. The principal cell of the lacrimal gland and primary contributor of proteins into ocular fluid is the lacrimal acinar cell. Disease-related changes in release of secretory products into ocular fluid imply, at some level, changes in the molecular mechanisms responsible for exocytosis at the apical plasma membrane of lacrimal acini. Our approach to the study of diseases affecting lacrimal gland secretory functions has therefore focused on elucidating the mechanisms responsible for accurate exocytotic release of secretory pro- ducts at the apical plasma membrane of healthy lacrimal acini, and to determine how changes in these mechanisms are related to the establishment and progression of lacrimal disease. Findings during the previous project period have defined the involvement of several key effectors of exocytosis including rab3D, vesicle-associated membrane protein 2, cytoplasmic dynein and actin filaments. Moreover, compensatory retrieval of acinar apical plasma membrane, essential for regeneration of secretory vesicles, utilizes a unique clathrin-mediated endocytotic mechanism involving actin, syndapins and N-WASP. Key questions regarding other fundamental mechanisms of lacrimal acinar exocytotic pathways remain unanswered, and will be addressed in Aims #1 and #2 using reconstituted primary rabbit lacrimal acini as an experimental model. To begin to address the changes in exocytotic pathways associated with initiation and progression of Sjogren's syndrome, Aim #3 probes age- and sex-related changes in organization and composition of the exocytotic pathway in lacrimal glands from control BALB/c mice as well as NOD mice, an experimental model of Sjogren's syndrome. Technically, these aims utilize an array of techniques including light and electron microscopy, biochemical analysis of subcellular membranes and proteomics. The specific aims are: Aim #1. Do lacrimal acinar cells contain distinct secretory vesicle populations? Aim #2. How do actin filaments facilitate exocytosis of secretory vesicles in lacrimal acinar cells? Aim #3. What components of the exocytotic pathway undergo age-related changes in lacrimal glands from BALB/c and NOD mice?

Grant: 3R01EY011386-08S1

Program Director: FISHER, RICHARD S

Principal Investigator: HAMM-ALVAREZ, SARAH F PHD

Title: Microtubule-based transport in lacrimal gland function

Institution: UNIV. OF SOUTHERN CALIFORNIA LOS ANGELES, CA

Project Period: 1996/07/01-2009/03/31

Abstract Text Not Available

Grant: 5R01EY009611-09

Program Director: KURINIJ, NATALIE

Principal Investigator: HANKINSON, SUSAN E MPH EPIDEMIOLOGY

Title: PROSPECTIVE STUDY OF RISK FACTORS FOR EYE DISEASE

Institution: BRIGHAM AND WOMEN'S HOSPITAL BOSTON, MA

Project Period: 1995/01/01-2005/12/31

We propose to investigate several lifestyle and genetic factors in relation to age-related macular degeneration (AMD) and primary open angle glaucoma (POAG) in two prospectively followed cohorts of women and men. Specifically, we will evaluate dietary intake of antioxidants and fat (including specific types of fat), postmenopausal hormone use and variants in the ATP-binding cassette-transporter retina (ABCR) gene in relation to both wet and dry AMD, and antioxidant intake, smoking, and systemic blood pressure in relation to POAG. The Nurses'Health Study (NHS) began in 1976 among 121,700 women ages 30-55 at that time. About 89,000 participants completed an extensively validated semiquantitative food frequency questionnaire (FFQ) in 1980 and every 2-4 years since. The Health Professionals Follow-up Study (HPFS) began in 1986 among 52,000 men ages 45-75, all of whom completed a FFQ at baseline and every four years since. Both groups have been sent a questionnaire biennially to update exposure information and reports of major illnesses, including AMD and POAG. Information has been collected repeatedly on specific vitamin supplement use, smoking, diagnosis of hypertension, reported blood pressure, and postmenopausal hormone use among other factors. Over 32,000 blood samples were collected in the NHS in 1989-90 and over 18,000 in the HPFS in 1993. In the proposed study we will confirm reports of AMD and POAG by contacting the participant's ophthalmologist, and obtaining detailed information from the optical record, including fundus photographs for those with AMD. A case will be considered to have AMD if it is judged to be sufficient to result in a visual acuity loss of at least 20/30 and is confirmed by a standardized review of the fundus photograph; wet and dry types will be carefully delineated by photographic review. A case will be considered to have POAG if confirmed by medical record review and is documented to have visual field loss. We anticipate 554 cases of exudative and 833 cases of dry AMD, and 1049 cases of POAG. Stratified and multivariate techniques will be used to quantify the risk of AMD and POAG according to the level of exposure after controlling for potentially important confounders; analyses will be conducted among participants who reported having a recent eye exam. Overall, the prospective design, large size of the cohorts, the high follow-up rates, repeated

exposure measures, and carefully confirmed disease definitions provide a unique opportunity to evaluate several hypotheses of public health importance.

Grant: 5R03EY014021-03

Program Director: FISHER, RICHARD S

Principal Investigator: JACOB, JEAN T PHD

Title: Capillary Electrophoresis Profiling of Tears in Dry Eye

Institution: LOUISIANA STATE UNIV HSC NEW ORLEANS NEW ORLEANS, LA

Project Period: 2002/05/01-2006/04/30

DESCRIPTION: (Applicant's Abstract) We propose to investigate and develop an inexpensive and reliable method to determine the lipid and protein composition of tears that could be used both in the basic science laboratory and clinically in a diagnostic laboratory setting. Our approach would not only generate the detailed information needed for more precise diagnosis of dry eye conditions, but also provide the basis for development of more specific and effective categories for (and possibly therapies targeted directly to) the individual deficiencies that 'characterize the spectrum of dry eye disorders. More than 12 million people in the United States alone have been clinically diagnosed with some form of keratitis sicca or dry eyes. Although their symptoms are similar, the underlying causes are often unknown and no practical methodology for evaluating the composition of tears from such patients exists. To date, analysis of tear composition has been hampered by the minute sample sizes available and the technical inability to identify and measure the components of such a complex fluid at concentration scales of nanomoles or less. Capillary electrophoresis-electrospray ionization mass spectrometry (CE-ESI/MS) is a sensitive, relatively inexpensive method capable of analyzing samples 2 pl or less in size. Using micellar electrokinetic capillary chromatography techniques coupled with mass spectrometry detection, we plan to design and develop 1) a novel standard separation method for the lipids within tears and 2) a novel standard separation method for the proteins within tears. We will then investigate the use of these methods to develop standard lipid and protein component profiles of normal tears and identify specific component differences in the tears from two different dry eye models. The development of this technology to provide specific information on the complex disorder know as dry eye could provide relief to and enhance the quality of life of millions of patients for whom no reliable long-lasting therapy is currently available.

Grant: 5R01EY010736-08

Program Director: FISHER, RICHARD S

Principal Investigator: JUMBLATT, MARCIA M

Title: Conjunctival Mucins:Synthesis and Function

Institution: UNIVERSITY OF LOUISVILLE LOUISVILLE, KY

Project Period: 1996/05/01-2005/08/31

Abstract Text Not Available

Grant: 5R01EY014102-04

Program Director: FISHER, RICHARD S

Principal Investigator: LANG, RICHARD A PHD

Title: Molecular Regulation of Lacrimal Gland Branching

Institution: CHILDREN'S HOSPITAL MED CTR

(CINCINNATI) CINCINNATI, OH

Project Period: 2001/09/30-2006/08/31

DESCRIPTION (provided by applicant): The condition of "dry eye" results from diminished production of the aqueous tear component. Some forms of dry eye are age-related and more common in females. Other manifestations of dry eye are associated with inflammatory disorders such as rheumatoid arthritis and Sjogren's syndrome. In rare cases there is a congenital absence of the lacrimal gland. Regardless of the etiology, in severe cases the absence of lubrication to the cornea can result in ulceration and blindness. The frequency of occurrence of dry eye means that it is a significant public health problem. Despite our long-standing knowledge of the dry eye condition and its potentially severe consequences, study of lacrimal gland development using techniques of modern molecular genetics has only recently been initiated. These studies took advantage of a transgene reporter that marked the epithelial component of the gland and allowed us to easily follow the process of budding and branching that occurs during development of the gland. Ultimately, this work showed that both the transcription factor Pax6 (expressed in gland epithelium) and the growth factor FGF10 (expressed in periorbital mesenchyme) were required for normal lacrimal gland development. With the current proposal, it is our intention to build on these studies and examine the role of the transcription factor Barx2, the bone morphogenetic proteins 4 and 7 and the adhesion molecule Ng-CAM in gland morphogenesis. The Specific Aims include (1) an examination of whether an FGF1O gradient is a controlling factor in gland morphogenesis, (2) a determination of how BMPs 4 and 7 can influence lacrimal gland morphogenesis, (3) loss-of-function experiments to determine whether the transcription factor Barx2 is required for gland morphogenesis, (4) an assessment of whether there is a regulatory relationship between Barx2 and the BMPs, and (5) a determination of whether Barx2 regulates the expression of the adhesion molecule LI. Combined, these will provide a focussed effort designed to answer questions central to the mechanism of lacrimal gland development and may provide an understanding of how to approach treatment of the dry eye condition.

Grant: 3R01EY013143-02S2

Program Director: FISHER, RICHARD S

Principal Investigator: LAURIE, GORDON W PHD ANATOMY

Title: Structure and Function of Ocular Lacritin

Institution: UNIVERSITY OF VIRGINIA CHARLOTTESVILLE

CHARLOTTESVILLE, VA

Project Period: 2002/08/01-2007/07/31

Abstract Text Not Available

Grant: 5R01EY013143-03

Program Director: FISHER, RICHARD S

Principal Investigator: LAURIE, GORDON W PHD ANATOMY

Title: Structure and Function of Ocular Lacritin

Institution: UNIVERSITY OF VIRGINIA CHARLOTTESVILLE
CHARLOTTESVILLE, VA

Project Period: 2002/08/01-2007/07/31

Our entirely rewritten application addresses the lacrimal/corneal axis as a fundamental regulator of ocular health. We seek a global understanding of how lacrimal acinar cell secretory control is governed and downstream consequences. Modulation of basal and reflex tear secretion is complex, largely unexplored and reversible; and plays into the enigmatic etiology of Dry Eye syndromes for which basal and reflex tearing capacity is often differentially deficient. Underlying main lacrimal gland 'basal'and 'reflex'tearing (terms that describe output at the ocular surface) are the acinar cell 'constitutive', 'constitutive-like', 'minor regulated'(basal) as well as 'major regulated'(reflex) secretory pathways - each with particular characteristics defined for the most part in other exocrine organs such as the parotid. Hypothetically possible is a receptor-mediated autocrine feedback loop(s) in which secretory product(s) released from one secretory pathway enhance or diminish secretion from another pathway, a potentially sensitive arrangement offering a novel framework for studying lacrimal hyposecretion in Dry Eye. Recently we discovered lacritin, an autocrine enhancer of lacrimal acinar cell basal secretion (Sanghi et al, J. Mol. Biol. '01; cover issue). Lacritin is highly conserved and released from lacrimal acinar cells by the major regulated pathway. It enhances basal tear secretion in a dose dependent manner, and rapidly activates both low amplitude calcium signaling and tyrosine phosphorylation. Lacritin also promotes the proliferation of downstream ductal cells and calcium signaling by corneal epithelial cells. Estimated cell binding affinity is 0.03 - 0.07 nM (versus NGF [0.01 - 1 nM], EGF [0.2 nM], PDGF [0.4 - 0. 7 nM]). Expression studies suggest that the lacritin gene is one of the most lacrimal gland-specific described. Our working hypothesis is that lacritin release stimulates the minor regulated pathway in a G -protein coupled receptor dependent manner, and that ligation of the same receptor in ductal and corneal epithelial cells regulates cell turnover. Our specific aims are therefore: (1) to identify and characterize how lacritin contacts target cell surfaces, (2) to clarify the identity of the lacritin-dependent secretory pathway, its mechanism of activation and significance, and (3) to elucidate lacritin's downstream ductal and ocular surface role.

Grant: 5R03EY014013-02

Program Director: FISHER, RICHARD S

Principal Investigator: MATHERS, WILLIAM D MD CLIN MEDICAL SCIENCES

Title: In Vivo Imaging of Leukocyte-Endothelial Dynamics

Institution: OREGON HEALTH & SCIENCE UNIVERSITY PORTLAND, OR

Project Period: 2003/04/15-2006/03/31

DESCRIPTION (provided by applicant): The process of leukocyte migration across the vascular endothelial barrier is fundamental to the process of inflammation and the response to infection. We will quantitate the effect of various medications such as topical corticosteroids, oral nonsteroidal anti-inflammatory drugs, and mast cell stabilizers in several of these processes. We have applied intravital microscopy in animal systems to visualize, quantitate and analyze this process. Recent advances in confocal microscopy have allowed a European group to quantitate leukocyte endothelial rolling and sticking in the microvasculature of the human eye. Combining our clinical expertise in confocal microscopy and our experience analyzing leukocyte vascular interactions, we propose to utilize in vivo confocal technology to quantitate leukocyte rolling and arrest in 4 different human vascular beds: the limbus, conjuctiva, episclera, and sclera. With these three specific aims: Aim one, we propose to image rolling and sticking of leukocytes in four different normal ocular vascular beds: the conjunctiva, limbus, episclera, and sclera. Aim two, we will compare leukocyte-endothelial dynamics in specific vascular beds in seven disease states: a) allergic seasonal conjunctivitis, b) Sjogren's syndrome and dry eye, c) blepharitis, d) graft versus host disease (GVHD), e) episcleritis, f) scleritis, and g) anterior uveitis. Aim three, we will determine the effect of medications including topical prednisolone acetate, a mast cell stabilizer (optipranolol), or an oral nonsteroidal anti-inflammatory drug (indomethacin) on endothelial-leukocyte dynamics in diseases for which each is frequently prescribed. Our studies will directly clarify the pathogenesis of several troublesome and rarely studied ocular disease processes. These studies will elucidate the mechanism by which medications alter these processes. Most importantly these studies will quantitate a fundamental human biological process in microvascular beds that have not previously been imaged.

Date Run: 03/16/05 **PUBLIC ABSTRACTS**

Grant:	5R01EY003177-24
Program Director:	LIBERMAN, ELLEN S
Principal Investigator:	MCAVOY, JOHNSTON W PHD OTHER AREAS
Title:	LENS DIFFERENTIATION & CATARACT: ROLE OF FGF, RA & WNT
Institution:	UNIVERSITY OF SYDNEY SYDNEY NSW,
Project Period:	1991/09/30-2007/07/31

DESCRIPTION (provided by applicant): This project aims to elucidate factors that regulate differentiation and growth of the epithelial monolayer. There is growing evidence that members of the FGF, RA and Wnt families may play key roles in lens epithelial cell biology. Part one is directed at testing the hypothesis that FGF (a low dose), RA and Wnt regulate lens epithelial proliferation, adhesion and communication. The effects of these ligands on expression of lens epithelial phenotypic characteristics including key molecules, such as cadherins, integrins and connexons, will be investigated using RT-PCR, in-situ hybridisation and immunohistochemistry. Part two will test the hypothesis that FGF (a low dose), RA and Wnt stimulate signalling cascades which cooperate to stimulate expression of key epithelial transcription factors. This will investigate modulation of receptor expression and identification of signaling cascades activated by these ligands. Transcription factors studied will be Pax-6, Eya-1, Six-3, maf-B, AP2a, RAR/RXR and Foxe-3. Part three will test the hypothesis that TFGbeta-induced cataractous changes involve inhibition of FGF, RA and Wnt signalling, and down regulation of expression of key epithelial transcription factors. This will investigate how TGFbeta modulates expression of FGF, RA and Wnt receptors, signalling molecules and transcription factors (see above). Part four will test the hypothesis that reduced Pax-6 expression makes lens epithelial cells more susceptible tp TGFbeta-induced cataractous changes. The small eye (Sey) mouse will be investigated to

determine if epithelial cells from this mutant are more sensitive to TGFbeta and, if so, the mechanism(s) involved. Understanding the molecular interactions that determine the lens epithelial phenotype is central to understanding the molecular basis of cataracts involving aberrant epithelial growth, including PCO.

Date Run: 03/16/05 **PUBLIC ABSTRACTS**

Grant: 3R01EY005801-19S1

Program Director: FISHER, RICHARD S

Principal Investigator: MIRCHEFF, AUSTIN K

Title: Basal-Lateral/Endomembrane Traffic in Lacrimal Acini

Institution: UNIVERSITY OF SOUTHERN CALIFORNIA LOS ANGELES, CA

Project Period: 1985/04/01-2004/09/29

Abstract Text Not Available

Date Run: 03/16/05 **PUBLIC ABSTRACTS**

Grant: 2R01EY005801-20

Program Director: FISHER, RICHARD S

Principal Investigator: MIRCHEFF, AUSTIN K

Title: Basal-Lateral/Endomembrane Traffic in Lacrimal Acini

Institution: UNIVERSITY OF SOUTHERN CALIFORNIA LOS ANGELES, CA

Project Period: 1985/04/01-2009/08/31

DESCRIPTION (provided by applicant): Sjogren's syndrome (SjS) and other immune-related diseases cause lacrimal dysfunction, impaired vision, and ocular surface inflammation in 2 to 4 million Americans. Primary lacrimal deficiency (PLD), which also may have an immune-related component, affects at least 6 million more. These concepts are unified by the hypothesis that: the milieu in the lacrimal glands reflects an immunohomeostasis involving regulatory lymphocytes, autoimmune effector lymphocytes, and secretory epithelial cells; lymphocyte and inflammatory cell mediators modulate epithelial cell functions; and the immunohomeostasis evolves in response to altered epithelial cell functions. However, little is known about the triggers that alter epithelial function to initiate the diseases, the reasons they occur more frequently in women than in men, and the molecular mechanisms that cause lacrimal dysfunction. The investigators have found that chronic stimulation of lacrimal acinar cells with the muscarinic receptor (MAChR) agonist, carbachol, causes epithelial secretory quiescence and also activates an aberrant endomembrane traffic program that blocks movement to lysosomes, potentially increasing exposure of constitutive autoantigens and initiating exposure of previously cryptic epitopes. The G proteins that classically couple to MAChR, Gq and G11, are shared by receptors for a wide variety of mediators, and their signaling is influenced by the sex hormones. Therefore, the investigators propose that: (a) physiological perturbations can initiate inappropriate Gq/G11 signaling that activates the aberrant traffic program, and (b) the local environments in SjS and PLD stimulate inappropriate Gq/G11 signaling that causes functional quiescence underlying lacrimal dysfunction. Specific Aim 1. What are the signals that activate the aberrant membrane traffic program? The central hypothesis is that MAChR remain activated and continue to activate Gq/G11. Specific Aim 2. Can chronic stimulation of other receptors also cause functional quiescence and activate the aberrant traffic program? The central hypothesis is that these changes can be elicited by agonists for receptors that utilize Gq/G11, including histamine, 5-hydroxytryptamine, PGE2, and estradiol. Specific Aim 3. What traffic effectors are responsible for the aberrant program? The central hypothesis is that chronic stimulation decreases dynein motor function but

increases p150(Glued) association with kinesin II, thereby increasing kinesin-mediated traffic. Specific Aim 4. How extensively does the aberrant program alter traffic of lysosomal proteins? The investigators will use a GFP-cathepsin S fusion protein and confocal microscopy to test the hypothesis that lysosomal proteins accumulate in the endosomes.

Grant: 5R03EY013720-03

Program Director: FISHER, RICHARD S

Principal Investigator: MIRCHEFF, AUSTIN K

Title: Prolactin--Autocrine/paracrine factor in lacrimal gland

Institution: UNIVERSITY OF SOUTHERN CALIFORNIA LOS ANGELES, CA

Project Period: 2002/05/01-2005/04/30

Dry eye is a common problem with a severe impact on the quality of life and potential vision-threatening complications. It often results from lacrimal insufficiency caused by immune-related processes, as in Sjogren's syndrome, or by hormone changes associated with aging and various physiological states. One critical hormonal influence on the lacrimal glands appears to be prolactin. Studies with human subjects, hypophysectomized rats, transgenic mice, and acinar cells in primary culture indicate that prolactin can impair lacrimal function, even at serum concentrations within the range of normal values. Moreover, the source of the prolactin that impairs lacrimal gland function may be the lacrimal glands themselves. The lacrimal glands express prolactin mRNA and protein, which may act as an autocrine or intracrine factor that in some circumstances may interfere with secretion. This project will use lacrimal acinar cells in primary culture to answer the following questions: 1. Does locally expressed prolactin act as an autocrine/intracrine factor that supports secretory functions at normal concentrations and impairs them at excessive concentrations? Neutralizing antibodies and antisense reagents will be used to minimize actions of locally expressed prolactin. Expression constructs will be used to overexpress prolactin. Acinar cell morphology, carbachol-induced protein secretion, expression of polymeric immunoglobulin receptors, and expression of ion transport proteins will be evaluated for changes related to altered prolactin expression. 2. Do altered forms of prolactin (16 kDa and phosphorylated 24 kDa) that have inhibitory effects in other cells inhibit lacrimal secretory function? The effects of overexpressed and added forms will be tested as in Specific Aim 1. 3. Does lacrimal prolactin act as a paracrine factor contributing to autoimmune activation? Antisense reagents and expression constructs will be used to suppress or enhance acinar cell prolactin expression, and the modified cells will be tested for their ability to promote proliferation of autologous lymphocytes in mixed cell reactions. This work will advance our understanding of significant mechanisms in lacrimal physiology, and it will have immediate implications for the direction of other studies now in progress. It also has the possibility of stimulating much work well beyond its present scope, including epidemiological studies aimed at identifying sub-populations of lacrimal deficiency patients with different etiologies, followed by design of appropriate, highly specific therapies.

Grant: 1R01EY015109-01

Program Director: LIBERMAN, ELLEN S

Principal Investigator: MITTAG, THOMAS W PHD BIOCHEMISTRY-UNSPEC

Title: Retinal ganglion cell loss in aging mice.

Institution: MOUNT SINAI SCHOOL OF MEDICINE OF NYU NEW YORK, NY

Project Period: 2004/07/10-2008/05/31

DESCRIPTION (provided by applicant): The primary aim of this project is to characterize the time-course and pattern of retinal ganglion cell (RGC) death in the highly inbred DBA 2J mouse and to establish this mouse as an in-vivo test system for potential neuroprotective interventions (drugs, gene-therapy, etc.). DBA/2 mice spontaneously develop a pigmentary glaucoma with elevated ocular pressure (IOP). There is a significant gender-difference in the time of onset and progression of retinal pathology. Severe IOP-induced loss of RGC occurs much earlier in life in the female DBA/2 mouse than the male or very old normal mice (C57 BL/6J). Experiments involving orchidectomy, supplementation with estrogen, testosterone or progesterone and chronic treatment with aromatase inhibitors are aimed to support the hypothesis that aromatase-derived estrogen (from testosterone) delays retinal pathology in male DBA/2 mice. The relationship of RGC loss to the elevated IOP history of individual eyes and to the degenerative changes in the superior colliculus of the brain receiving input from that eye will also be investigated. Mice chronically treated (3-4 months) with several classes of drugs that are partially effective in short-term treatments of acute induced rat RGC death models, will be evaluated by mapping of RGC in the entire retina. The classes of drugs to be tested include an alpha-adrenergic agonist, a beta-adrenergic antagonist, inhibitors of the NOS-2 enzyme, and the anti-Parkinson's agents deprenyl and memantine. The drug experiments are aimed at establishing proof-of-principle that agents having neuroprotective properties in cultures or acute model systems can be effective in a slow, spontaneous neurodegenerative condition, such as RGC death, when administered as chronic systemic therapy.

Grant: 5K23EY013766-03

Program Director: REDFORD, MARYANN

Principal Investigator: NICHOLS, JASON J

OD OPTOMETRY

Title: The Contact Lens and Dry Eye Study

Institution: OHIO STATE UNIVERSITY COLUMBUS, OH

Project Period: 2002/02/01-2007/01/31

The primary goal of this K23 proposal is to train the Jason J. Nichols, OD MS is an independent clinician-scientist. To achieve this goal, a five-year training program is proposed which emphasizes mentoring and formal coursework in 1) vision science leading to a PhD from The Ohio State University College of Optometry and in 2) biostatistics and epidemiology leading to an MPH degree from The Ohio State University College of Medicine and Public Health. In 1995, the National Eye Institute (NEI) sponsored dry eye workshop report identified contact lens-related dry eye as a major sub-classification of dry eye syndrome. Yet, there has been little clinical research sponsored by the NEI to study the etiology or epidemiology of contact lens-related dry eyes since that time. The proposed training will provide Dr. Nichols with the necessary patient-oriented research skills to conduct an epidemiologic study of contact lens-related dry eye, which has been carefully designed to complement and enhance those skills obtained during the development period. Contact lens-related dry eye may severely impact ocular health by leading

to desiccation of the corneal epithelium or an increased incidence of infectious disease. The relation between contact lens dehydration and evaporative changes in the tear film needs to be understood as they may be the primary cause of contact lens-related dry eye. A cross-sectional/nested case-control study will be conducted and the analyses will address risk factors thought to be associated with contact lens-related dry eye. In the cross-sectional phase of the study (Phase I), we will characterize and elucidate the functional significance of the discrepancy between the frequency and severity of dry eye symptoms during contact lens wear. In the nested case-control phase of the study (Phase II), we will test the hypothesis that evaporative factors including contact lens characteristics, tear film changes, Meibomian gland disease, and blanking patterns are associated with an increased risk for contact lens-related dry eye. The long-term objective of this research is to contribute to a better understanding of the etiology and risk factors for contact lens-related dry eye so that progress can be made toward its prevention.

Grant: 5U10EY012118-05

Program Director: DUDLEY, PETER A

Principal Investigator: PERICAK-VANCE, MARGARET A PHD :HUMAN GENETICS

Title: UNIFYING GENETICS EPIDEMIOLOGY OF MACULAR DEGENERATION

Institution: DUKE UNIVERSITY DURHAM, NC

Project Period: 2000/06/15-2005/05/31

Age-related macular degeneration (AMD) is the most common cause of severe vision loss among individuals over age 50 in the U.S. The socioeconomic impact is considerable, and is expected to become greater as the U.S. population ages. Unfortunately, treatment options remain limited because the etiology of this devastating disease remains unknown. Considerable evidence implicates a combination of genetic, environmental, and biological factors in the pathogenesis of AMD as such suggested genetic effect involves the ATP-binding transporter (ABCR) gene. We thus hypothesize that underlying susceptibility gene(s) are critical to the development of AMD, and likely interact with environmental factors to trigger both the development and progression of the disease. The purpose of this study is to elucidate the genetic susceptibility to the development of AMD and to analyze the interaction of these genes with environmental influences. We will use both candidate gene and genomic screening approaches to identify these genes. Already identified genetic and environmental risk factors will be evaluated and current statistical methodologies will be adapted to examine the possible interactions. Multiplex (greater than 1 AMD affected/family) families will be recruited for the genetic analyses and detailed risk factor information will be collected on all study participants. Family-based association methods will be used to evaluate candidate genes, environmental risk factors and gene- gene and gene-environment interactions. The information derived from this study will further our understanding of this complex disease. The identification of specific susceptibility genes and evaluation of gene-environment interaction will be crucial for future studies in unraveling the etiology of AMD and developing better treatments.

Grant: 5R01EY011915-07

Program Director: FISHER, RICHARD S

Principal Investigator: PFLUGFELDER, STEPHEN MD

Title: Pathogenesis of Conjunctival Squamous

Institution: BAYLOR COLLEGE OF MEDICINE HOUSTON, TX

Project Period: 1997/08/01-2006/03/31

DESCRIPTION (provided by applicant): Our research has identified that changes in the ocular surface environment of dry eye, such as a hyperosmolar tear film, stimulate the production of pro-inflammatory cytokines by the ocular surface epithelia. Our preliminary data suggests that these cytokines, particularly interleukin-1 (IL-1) and TNF-alpha, may play a key role in the pathogenesis of the epithelial and immuno-pathology of keratoconjunctivitis sicca, (KCS) the ocular surface disease of dry eye. Four proposed Specific Aims will test this theory. Aim I will confirm whether experimentally induced dry eye in mice stimulates the production and release of pro-inflammatory cytokines by the ocular surface epithelium that promote ocular surface inflammation and KCS. Aim 2 will determine whether hyperosmolar stress stimulates the production of pro-inflammatory cytokines by the ocular surface epithelium by activating the p38 stress activated protein kinase pathway. Aim 3 will study the expression of IL-1 and TNF-alpha receptors on the ocular surface and determine if there are differences in the expression of these receptors and their soluble antagonists between normal and dry eyes. Aim 4 will investigate the effects of the pro-inflammatory cytokines of dry eye on the expression of matrix metalloproteinase enzymes (MMPs) and mucins on the ocular surface. These factors that have been implicated in the disruption of ocular surface barrier function and homeostasis in KCS. These studies will provide clinically relevant information regarding the role of inflammation and its cytokine mediators on the pathogenesis of the ocular surface disease of dry eye, a condition experienced by over 10 percent of the population over the age of 30.

Date Run: 03/16/05 **PUBLIC ABSTRACTS**

Grant: 5R01EY010550-09

Program Director: FISHER, RICHARD S

Principal Investigator: SCHECHTER, JOEL E

Title: Prolactin as a Lacrimal Gland Immunoregulator

Institution: UNIVERSITY OF SOUTHERN CALIFORNIA LOS ANGELES, CA

Project Period: 1994/04/01-2006/12/31

Abstract Text Not Available

Date Run: 03/16/05 **PUBLIC ABSTRACTS**

Grant: 3R01EY010550-09S1

Program Director: FISHER, RICHARD S

Principal Investigator: SCHECHTER, JOEL E

Title: Prolactin as a Lacrimal Gland Immunoregulator

Institution: UNIVERSITY OF SOUTHERN CALIFORNIA LOS ANGELES, CA

Project Period: 1994/04/01-2006/12/31

Abstract Text Not Available

Grant: 1R41EY015376-01

Program Director: HELMSEN, RALPH J

Principal Investigator: SHEPPARD, JOHN D MD

Title: Stimulation of Tear Secretion by a Novel Glycoprotein

Institution: EYERX RESEARCH, INC. NORFOLK, VA

Project Period: 2004/09/30-2005/09/29

DESCRIPTION (provided by applicant): Dry eye is a ubiquitous, often overlooked, underdiagnosed and poorly understood affliction of the ocular surface. This common opthalmological complaint can markedly affect a patient's quality of life. As a multifactorial disease, dry eye has hyposecretory, auto-immune, inflammatory, hormonal, neurogenic, toxic, and iatrogenic components. Common to all etiologies is a decrease in both volume and quality of tear secretion. Current therapy ranges from topical application of aqueous, oil and gel tear film constituent replacement "artificial" tears, to topical anti-inflammatory drugs, to oral secretagogues. There are currently no approved topical agents indicated for enhancement of tear flow and production, which would address the primary defect in aqueous deficiency dry eye disease. Lacritin is a stable, novel human tear glycoprotein produced solely by lacrimal and salivary glands. It binds to and stimulates a rapid, sustained release of calcium in cultured corneal epithelial cells, which suggests topical application of lacritin may stimulate the cornea/lacrimal gland axis to increase tear production. Based upon these properties elucidated in cell culture, we hypothesize that lacritin has potential as a therapeutic agent to promote tear production. Compared to current therapy, as an ocular-specific prosecretory glycoprotein, lacritin has a unique mechanism of action. We expect that topical application of lacritin will increase tear production by stimulation of the lacrimal gland/corneal axis. The long-term goals of this translational research project are to develop lacritin as an efficacious, nontoxic topical treatment. Specific aims for this proposal are (1) demonstration, using an in vivo rabbit model, of the ability of lacritin to increase tear production after topical administration, (2) determination of the effect of lacritin on the normal composition of tears, and (3) examination of lacritin-treated ocular tissues for signs of adverse effects. The primary outcome measurement is lacritin's ability to increase tear production. In vivo analysis also includes confocal microscopy, slit lamp biomicroscopy, digital photography, application of the MacDonald-Shadduck Scale for Ocular Toxicity, tear break up time, vital dye assessment with fluorescein and Lissamine green, and Schirmer's test for tear production.

Grant: 5R21EY015671-02

Program Director: SHEN, GRACE L

Principal Investigator: SOSNE, GABRIEL MD

Title: Thymosin beta 4 and Autoimmune Ocular Surface Disease

Institution: WAYNE STATE UNIVERSITY DETROIT, MI

Project Period: 2003/09/30-2005/08/31

DESCRIPTION (provided by applicant): Keratoconjunctitivitis sicca (KCS), or dry eye disease, is one of the most common conditions seen by ophthalmologists and affects 15% of those from 65-84 years of age, or 4.3 million Americans. The pathophysiology of dry eye includes immune-mediated inflammation involving both the ocular surface and the lacrimal gland. While knowledge of the pathology of dry eye

disease has improved significantly during recent years, the mainstay of treatment, ocular lubrication, provides only palliative relief at best to patients with severe dry eye disease. Therefore, attention has turned to immunomodulation as a therapeutic approach for I severe dry eye disease, especially for that seen in autoimmune diseases like Sjogren's syndrome, I rheumatoid arthritis, and systemic lupus erythematosus (SLE). Available agents such as corticosteroids have I considerable side effects that render them therapeutically impotent in a number of patients. Recently, the FDA approved Cyclosporine A (CSA), 0.5% (Restasis) for the treatment of moderate to severe dry eye. However, 85% of CSA-treated patients did not experience a significant increase in tear production. Therefore, a therapeutic agent that could reliably decrease immune-mediated ocular surface damage without significant adverse effects in a large proportion of affected patients would constitute a major therapeutic advance, particularly for dry eye disease. Thymosin beta 4 (Tb4) promotes corneal wound healing and reduces inflammation in mice after chemical injury to the eye. Since Tb4 has both anti-inflammatory and wound healing properties, it is an ideal candidate for evaluation in an autoimmune model of dry eye. Two specific aims are proposed to test the overall hypothesis of this application that Tb4 modulates lacrimal gland, corneal and conjunctival inflammation in an animal model of autoimmune dry eye disease. 1) To test the hypothesis that Tb4 alters production of cytokines, chemokines and specific matrix metalloproteinases (MMPs) in a murine model of Sjogren's syndrome; 2) To test the hypothesis that Tb4 alters autoimmune ocular surface damage in the MRL/Ipr mouse by decreasing lacrimal gland inflammation and conjunctival squamous metaplasia. By identifying Tb4 as a novel wound healing and anti-inflammatory agent to protect the ocular surface from inflammatory and immune tissue injury, it is aimed to substantiate the potential clinical usage of Tb4 for the majority of patients who are not relieved by currently available therapies.

Grant:	1R03EY015115-01	
Program Director:	LIBERMAN, ELLEN S	
Principal Investigator:	STAMER, W DANIEL	PHD PHARMACOLOGY
Title:	SELENIUM-INDUCED GLAUCOMA	
Institution:	UNIVERSITY OF ARIZONA	TUCSON, AZ
Project Period:	2003/12/01-2006/11/30	

DESCRIPTION (provided by applicant): Glaucoma, the second leading cause of irreversible blindness in the United States, is a group of disorders characterized by a progressive loss of retinal ganglion cells with associated loss of vision that is in most cases coincident with elevated intraocular pressure (IOP). Today and in the foreseeable future, those with glaucoma are clinically managed with pharmaceutical agents that lower IOP. Elevated IOP in those with glaucoma results from defective regulatory processes in the outflow pathway. Consequently, a current area of focus for glaucoma research and a program priority area for the National Eye Institute (Glaucoma Panel Program Objective #3) is to understand the molecular and cellular mechanisms that underlie the regulation of fluid flow through the human outflow pathway. During a recent safety review in a current selenium-supplementation intervention trial (the Nutritional Prevention of Cancer Trial) an increased incidence of primary open-angle glaucoma amongst participants, particularly women, in the selenium treatment group was uncovered. In the present proposal, we examine the effects of selenium on the biology of human trabecular meshwork cells and outflow function both in the presence and absence of 17 beta-estradiol. Hypothesized effects of selenium on outflow function are consistent with demonstrated effects of selenium on other cell types that include alterations in extracellular matrix turnover, cell cycle arrest and induction of apoptosis. The present study will examine these endpoints in cell and organ culture models and thus is innovative for at least two reasons: First,

determination of selenium effects on cell biology in human outflow pathway will provide insight into and/or support for critical regulatory mechanisms that control outflow facility. Second, selenium treatment of outflow tissues may provide a novel glaucoma model to study changes in the outflow pathways at the molecular and cellular level in a controlled manner. If successful, results obtained from these investigations will provide a basic understanding of selenium effects on aqueous outflow facility, uncover novel therapeutic targets for glaucoma treatment and generate a foundation for future investigations.

Grant:	5R01EY005612-18	
Program Director:	FISHER, RICHARD S	
Principal Investigator:	SULLIVAN, DAVID A	PHD
Title:	Gender, sex steroids and dry eye syndromes	
Institution:	SCHEPENS EYE RESEARCH INSTITUTE	BOSTON, MA
Project Period:	1985/09/30-2005/11/30	

DESCRIPTION (provided by applicant): The preocular tear film plays a critical role in maintaining ocular surface integrity, protecting against microbial challenge and preserving visual acuity. Tear film dysfunction, in turn, may severely impact the eye and lead to desiccation of the corneal epithelium, ulceration and perforation of the cornea, an increased incidence of infectious disease, and pronounced visual impairment and blindness. Countless people suffer from tear film disorders, which are termed dry eye syndromes and are classified into 2 major types: aqueous-deficient and evaporative. Aqueous-deficient dry eye is due to decreased tear secretion from the lacrimal gland. An example is Sjogren's syndrome, a common autoimmune disease that afflicts primarily women and destroys the lacrimal gland. Evaporative dry eye is typically caused by meibomian gland dysfunction and may be a major cause of dry eye during menopause, use of estrogen hormone replacement therapy (HRT) and aging. The long range objectives of this grant application are to test our hypotheses that: (1) sex steroids are extremely important in the physiological regulation of the lacrimal and meibomian glands, as well as the production of the tear film; and (2) gender, sex steroid hormones, and in particular androgen deficiency, are critical etiologic factors in the pathogenesis of both aqueous-deficient and evaporative dry eye syndromes. Experimental procedures include mouse models, DNA hybridization arrays (i.e. gene chips), RT-PCR, ribonuclease protection assays, Northern, slot and Southern blots, in situ hybridization, cell cultures, immunoassays, HPLC/mass spectrometry, enzyme assays, histology, image analysis, hormone reconstitution experiments, as well as clinical studies with humans. Our specific aims are to: (1) identify the genes and proteins that mediate the gender-related differences in, and the sex steroid control of, lacrimal glands in normal and autoimmune (i.e. Sjogren's syndrome) mice; (2) identify the genes and proteins involved in the gender-associated variations in, and the sex steroid regulation of, the mouse meibomian gland; and (3) determine the specific effects of HRT use (estrogen, or estrogen plus progesterone), with or without androgen supplementation, on the ocular surface of postmenopausal women. Results from the studies should significantly advance our understanding of the processes by which gender and sex steroids influence the anterior segment of the eye. In addition, findings may have health relatedness for the eye, because they: (1) explore the regulation of the tear film; and (2) may lead to the development of specific therapies for the clinical treatment of dry eye syndromes.

Grant: 2R01EY012689-04A2

Program Director: SHEN, GRACE L

Principal Investigator: TROUSDALE, MELVIN D

Title: Anti-Inflammatory Genes in Autoimmune Dacryoadenitis

Institution: DOHENY EYE INSTITUTE LOS ANGELES, CA

Project Period: 2000/05/01-2009/06/30

DESCRIPTION (provided by applicant): Dry eye affects approximately 10 million Americans, most of whom are women. An estimated 2 million cases of Sjogren's syndrome exist in America. Our long-term goal is to elucidate the mechanism of immunopathogenesis of autoimmune dacryoadenitis and to determine the impact of vlL-10 and TNF-inhibitor gene expression on the disease. In an in vivo rabbit model of autoimmune dacryoadenitis, lymphocytes proliferate in a mixed cell reaction with purified autologous lacrimal gland epithelial cells and, when injected back into the rabbit's own contralateral gland, induce intense focal lymphocytic infiltration, thus creating a model for autoimmune dacryoadenitis. Tear production is reduced and tear stability is decreased in the dysfunctional lacrimal gland while rose bengal staining of the corneal surface is increased. CD4+ T cells and CD18+ cells increase significantly in the immune infiltrates in the gland, and the CD4+ to CD8+ T cell ratio increases as it does in Sjogren's syndrome. Aim 1. Characterize the cells that proliferate in autologous mixed cell reactions. Hypothesis 1a. Autoreactive CD4+ T cells proliferate in the mixed cell reaction and secrete proinflammatory cytokines (e.g. IL-2, TNF b, and IFNy,). Hypothesis 1b. Lacrimal autoimmunity is a normal phenomenon and active functioning regulatory T cells ordinarily prevent normal autoimmunity from developing into clinical disease. Aim 2. Identify the autoreactive T cell responsible for inducing autoimmune dacryoadenitis and monitor the progression of the disease. Hypothesis 2a. Purified lymphocyte population that proliferate in mixed cell reactions induce autoimmune dacryoadenitis. Hypothesis 2b. Autoimmune dacryoadenitis can be induced by the animal's own activated lymphocytes administered at sites other than the lacrimal gland (e.g. intravenous or subcutaneous), and this will result in systemic disease involving the salivary glands and kidneys. Aim 3. Develop gene transfer therapeutic strategies using an AAV vector (AAV-tetON-vlL- 10) with an inducible promoter for treating autoimmune dacryoadenitis and explain the mechanism of action of vlL-10 on effector T cells. Hypothesis 3a. Long-term expression of vlL-10 gene in the lacrimal gland suppresses effector T cell (e.g. CD4+ cells) proliferation, but not suppressor T cell activity. Hypothesis 3b. vlL-10 suppresses CD4+ T cell proliferation by down regulating expression of Th 1 cytokines IL-2, TNF-b and interferon-y. Aim 4. Elucidate the exit pathway of transgene product from the transduced acinar cell. Hypothesis 4a. Intracellular trafficking of vlL-10 results in the anti-inflammatory cytokine exiting the transduced lacrimal cells via both apical and basolateral membranes. The overall study will determine the effector cell phenotype, their secreted proinflammatory cytokines and the impact of over expression of vlL-10 on Th 1, Th2 and Th3 responses during progression and regression of the autoimune disease.

Grant: 3R01EY010056-10S1

Program Director: FISHER, RICHARD S

Principal Investigator: WILSON, STEVEN E MD

Title: CORNEAL EPITHELIAL CELL GROWTH FACTORS AND RECEPTORS

Institution: CLEVELAND CLINIC LERNER COL/MED-CWRU Nashville,, TN

Project Period: 1994/08/01-2005/06/30

Abstract Text Not Available

Date Run: 03/16/05 **PUBLIC ABSTRACTS**

Grant: 1R21EY015457-01

Program Director: FISHER, RICHARD S

Principal Investigator: YIU, SAMUEL C PHD

Title: Bioartificial Lacrimal Gland

Institution: DOHENY EYE INSTITUTE LOS ANGELES, CA

Project Period: 2004/05/01-2006/04/30

DESCRIPTION (provided by applicant) Millions of Americans have dry eye disease. Individuals plagued by the discomfort, burning, irritation, photophobia, and other symptoms of dry eye disease also have blurred vision, contact lens intolerance, the inability to produce emotional tears, and an increased risk of ocular surface damage and infection. In the United States alone an estimated 2 million Sjogren's Syndrome patients have dysfunctional lacrimal glands and severe dry eye and there is no satisfactory treatment. A bioartificial lacrimal gland would greatly benefit these patients. The new field of tissue engineering has built on the interface between materials science and biocompatibility to create the possibility of developing a bioartificial lacrimal gland. Our three specific aims are: 1) To identify the optimal biomaterials for use as the substrate for the growth of rabbit lacrimal epithelial cells in a three-dimensional scaffold. 2) To test the physiological properties of these bioengineered tissues, including secretory functions and electrophysiological activities. 3) To establish strategies and data for the design and development of a bioartifical lacrimal gland as the basis for a BRG grant proposal using the RO1 funding mechanism. This work will advance our understanding of how lacrimal epithelial cells function in this artificial environment and lead to the development of an RO1 proposal. Ultimately, we envision a bioengineered lacrimal gland system, to be surgically implanted in periocular tissues that will produce sufficient tear flow to maintain the health of the ocular surface. Such a device could relieve the symptoms of millions of dry eye patients; and it could possibly make obsolete the frequent daily use of lubricant eye drops, saving patients the time and effort of medication use and saving millions of dollars annually in the purchase of lubricating eye drops.

Date Run: 03/16/05 **PUBLIC ABSTRACTS**

Grant: 1R03EY015134-01

Program Director: FISHER, RICHARD S

Principal Investigator: YOUNG, WILLIAM W PHD

Title: OCULAR SURFACE MUCIN ppGaNTase GLYCOSYLTRANFERASES

Institution: UNIVERSITY OF LOUISVILLE LOUISVILLE, KY

Project Period: 2004/05/01-2007/04/30

DESCRIPTION (provided by applicant): The mucus layer, secreted primarily by the conjunctival goblet cells but also by the corneal and conjunctival epithelia, is a critical protective layer for the ocular surface; shielding it from pathogenic and environmental challenges. Mucins are a heterogeneous group of highly glycosylated proteins that are present both on the ocular surface cells and as major soluble components of tear fluid. The first and rate-limiting step of O-glycosylation of mucins requires the action of at least one

isoform of the UDPGalNAc: polypeptide N-Acetylgalactosaminyltransferase (ppGaNTase) family of glycosyltransferases. Without glycosylation, mucins would lack the viscoelastic properties required for proper function. The hypothesis of this project is that one cause of dry eye disease is abnormal mucin glycosylation due to altered expression of ppGaNTase isoforms. In the first aim we will compare the levels of mRNA expression of ppGaNTase isoforms in normal and dry eye patients by real-time PCR using the Taqman technique. The results will provide the first complete analysis of the expression of this critical glycosyltransferase family in human ocular tissues and point to one possible cause of human dry eye disease. In the second aim we will determine which ppGaNTase isoforms are responsible for glycosylation of specific mucin types using RNA interference and inhibitors of ppGaNTase action. First, we will determine which ppGaNTase isoforms are expressed at the mRNA level in human corneal and conjuncrival cell lines by real-time PCR. Second, we will use gene silencing by small interfering RNAs (siRNA) to specifically silence each ppGaNTase isoform and then determine by Western blotting whether silencing of one ppGaNTase isoform results in altered glycosylation of each mucin type. As a positive control for ablation of mucin glycosylation, we will treat cells with inhibitors of the ppGaNTase family. The results of RNA interference will enable us to obtain the first evidence in whole ocular cells as to which ppGaNTase isoforms are required for the glycosylation of particular mucin types.

Grant: 5R01EY012383-06

Program Director: SHEN, GRACE L

Principal Investigator: ZOUKHRI, DRISS PHD MEDICINE AND IMMUNOLOGY

Title: Stimulus-Secretion Coupling in Diseased Lacrimal Gland

Institution: TUFTS UNIVERSITY BOSTON BOSTON, MA

Project Period: 1999/01/01-2007/07/31

DESCRIPTION (provided by applicant): Sjogren's syndrome, a systemic inflammatory autoimmune disease which occurs almost exclusively in females, is the leading cause of aqueous tear deficient dry eye. To date there is no cure for this disease and the precise mechanisms responsible for the decreased tear secretion are largely unknown. Studies from this laboratory point to a potentially pivotal role of the proinflammatory cytokines, interleukin-1alpha (IL-1a), IL-1beta (IL-lb), and tumor necrosis alpha (TNFa), in the impaired function of the lacrimal gland associated with Sjogren's syndrome. Specifically, we found that these cytokines have a dual target in the lacrimal gland: the nerve endings (i.e., inhibition of neurotransmitter release) and the epithelial cells (i.e., inhibition of lacrimal gland protein secretion). However, the mechanism(s) by which these cytokines interfere with lacrimal gland nerve endings and lacrimal gland acinar epithelial cell functions remain to be elucidated. Thus, the long term objective of the present proposal is to define the intracellular signaling pathways activated by proinflammatory stimuli to inhibit lacrimal gland secretion. A second objective is to test the effects of selective inhibitors of these pathways on lacrimal gland secretion using a murine model of Sjogren's syndrome. To obtain these goals, the following specific aims have been proposed: (1) define the signaling pathways activated by inflammatory stimuli to inhibit neurotransmitter release and lacrimal gland secretion; (2) determine if JNK, ERK, and iNOS are involved in the impaired lacrimal gland secretion associated with Sjogren's syndrome; and (3) determine if ICE activity is necessary for inflammation-induced inhibition of neurotransmitter release and lacrimal gland secretion. Lacrimal gland slices will be prepared from diseased and control female mice. Activation of JNK, ERK, and iNOS will be measured by western blotting. The release of neurotransmitter from lacrimal gland nerve endings and protein secretion will be

measured spetrophotometrically. Selective inhibitors of JNK, ERK, and/or iNOS will be given subcutaneously to diseased and control female mice.

Grant: 3R01EY012383-06S1

Program Director: SHEN, GRACE L

Principal Investigator: ZOUKHRI, DRISS PHD MEDICINE AND IMMUNOLOGY

Title: Stimulus-Secretion Coupling in Diseased Lacrimal Gland

Institution: TUFTS UNIVERSITY BOSTON BOSTON, MA

Project Period: 1999/01/01-2005/07/31

Abstract Text Not Available

Project Number: 1 Z01 EY000312-08
LBC: LMOD
Title: Estradiol Prevents Cataracts in Female But Not Male Lenses
HN or SAC code: HNW299
PI(s): Deborah A. Carper, PhD (MT , NEI)
Keywords: cataract, transforming growth factor-beta, alpha smooth muscle actin, estrogen

SUMMARY: Age-related cataracts occur more frequently in women than in men of comparable age. It is believed that this is due to the loss of estrogen after menopause. Support for this hypothesis comes from epidemiological studies, which show that hormone replacement therapy reduces the risk of cataract, and from animal studies, which show that estradiol prevents TGF-beta-induced anterior subcapsular cataracts in ovariectomized rats. We extended the latter observation by testing whether estradiol protects against TGF-beta-induced cataracts in lenses from normal male and female rats. Our results showed that in the presence of low concentrations of TGF-beta2 (0.15 ng/ml), cultured male rat lenses developed twice as many cataract plaques as female rat lenses. Estradiol (10-8M) prevented cataracts in female lenses, but not male lenses. In parallel, the anterior subcapsular cataract marker, alpha-smooth muscle actin, was up regulated in both male and female rat lenses, but down regulated only in female lenses in the presence of estradiol. These findings suggest that there may be sex-specific differences in the levels of estrogen receptors. TGF-beta2-induced cataracts serve as a model of human anterior subcapsular cataracts and secondary cataracts, with many phenotypic and biochemical similarities. The results of our study suggest that estradiol could be a therapeutic option, although, the sex-related response must first be tested in human lenses.

Project Number: 1 Z01 EY000367-05
LBC: DIR
Title: Ocular Surface Disease
HN or SAC code: HNW4

Lead Investigator(s): Janine A. Smith, MD (DECR , NEI)
Supervisor of Record: Sheldon S Miller , Ph.D. (DIR , NEI)
Keywords: Dry eye, keratoconjunctivitis sicca,Sjogren's Syndrome, Premature Ovarian Failure, Cyclosporine A, cornea

SUMMARY: This program is focused upon ocular surface immune-mediated diseases. We recently completed a masked trial of Cyclosporine eye drops for the treatment of keratoconjunctivitis sicca. We found elevated and comparable conjunctival inflammatory cell sub-populations and markers of immune activation (MHC Class II and adhesion molecules) in patients with both Sjogrens' Syndrome, a systemic autoimmune disease, aas well as, in the common form of dry eye. Our research has provided tangible evidence of an inflammatory basis for dry eye and confirms the rationale of anti-inflammatory therapy for its treatment, which represents a significant change in treatment strategy for this disease. We have also reported several of our findings on the immunopathogenesis of conjunctival manifestations of keratoconjunctivitis sicca. In addition, we have published a novel manifestation of Wegener's granulomatosis, tarsal-conjunctival disease which is characterized by signficant conjunctival cicatrization, scarring and increased risk of visual loss. We have also been investigating the treatment of the autoimmune exocrinopathy, Sjogren's Syndrome, which is associated with a particularly severe form of dry eye, in collaboration with the NIDCR, in 3 masked, placebo-controlled trials of DHEA, Thalidomide and Etanercept treatment. All 3 trials have been completed and the papers submitted for publication. In addition, we have also continued to work on validation of outcome measures for ocular surface disease and have published our findings which willfacilitate the use of ocular surface vital dye staining as an outcome measure for clinical trials. This work is ongoing. In addtion, we have also identified women with Premature Ovarian Failure as a new population of patients at risk for the development of ocular surface disease. Compared to age-matched women, significantly more patients with Premature Ovarian Failure use ocular lubricants and have objective signs and symptoms of dry eye. These patients scored significantly worse than controls on all 3 symptom questionnaires used and showed significantly more eye damage measured by ocular surface vital dye staining using validated grading schemes. These findings suggest that the dysregulation of hormones and immunologic dysfunction seen in Premature Ovarian Failure may play a role in the pathogenesis of ocular surface disease in these patients. This paper has been accepted for publication by Archives of Ophthalmology.

National Heart, Lung, and Blood Institute

(NHLBI)

National Heart, Lung, and Blood Institute

Menopause-Related Research

Because many of the diseases and conditions that fall within the NHLBI mandate (e.g., coronary disease, hypertension, congestive heart failure, chronic obstructive pulmonary disease) primarily affect older people, many postmenopausal women are being studied in the Institute's clinical research programs. This document focuses specifically on NHLBI-supported research in women that is related to reproductive hormonal status or to changes in health risks that occur as women pass through menopause.

Women's Health Initiative

The Women's Health Initiative (WHI) is a complex multicenter project examining strategies for the prevention and control of the most common causes of death, disability, and impaired quality of life among postmenopausal women, including cardiovascular disease, breast and colorectal cancers, and osteoporotic fractures. Initiated in 1991 with planned completion in 2007, the WHI is conducted as a consortium effort led by the NHLBI in cooperation with the Office of Research on Women's Health, the National Cancer Institute, and the National Institute of Arthritis and Musculoskeletal Diseases. Recruitment was completed in 1998. Over 68,000 women of diverse racial, ethnic, geographic, and socioeconomic background are participating in three overlapping randomized controlled Clinical Trials (CT), and an additional 93,676 women are enrolled in a parallel Observational Study (OS). A third component, the Community Prevention Study, focused on community-based prevention strategies to enhance adoption of healthful behaviors and was conducted by the Centers for Disease Control and Prevention.

Clinical Trials

The CT component is designed to evaluate the effect of:

1) **Low-fat eating pattern** in preventing breast and colorectal cancers.
2) **Postmenopausal hormone therapy** in preventing coronary heart disease and other cardiovascular diseases, with breast cancer as a possible adverse outcome. The estrogen-plus-progestin component of the hormone trial was stopped on July 9, 2002, because WHI researchers found that the risks of long-term estrogen-plus-progestin therapy outweigh its protective benefits. NIH stopped the estrogen-only component on February 29, 2004 because of increased risk for stroke and no benefit for coronary heart disease. (See publications for related papers.)
3) **Calcium and vitamin D supplementation** in preventing osteoporotic fractures and colorectal cancer.

Observational Study

The OS is identifying predictors of disease by: 1) examining the associations of known or putative risk factors (including biomarkers) to disease status at baseline and during follow-up; 2) seeking to find new risk factors using the stored biological samples and data as a resource; and 3) examining the effects of change in known or putative risk factors on disease outcome.

A detailed description of the WHI is available in *Controlled Clinical Trials* 1998;19:61 – 109. A list of publications from the WHI can be found at http://www.nhlbi.nih.gov/whi/references.htm.

Representative NHLBI Research Projects in FY 2004

Project No.	Title	Investigator	Institution
R01 HL028266	Epidemiology of Cardiovascular Risk Factors in Women	Kuller	U. Pittsburgh

A long-term investigation of the evolution of cardiovascular risk factors and subclinical cardiovascular disease from premenopause through menopause.

R01 HL032050	Caffeine Influences on Exercise and Psychological Stress	Lovallo	U. Oklahoma

An evaluation of the effects of caffeine intake on blood pressure and cortisol secretion, under conditions of mental and exercise stress, with an emphasis on variations in response as women enter menopause.

R01 HL033177	Positron Tomography in Ischemic Heart Disease	Schelbert	UCLA

A study of coronary vasomotor function that, in postmenopausal women, will explore protective effects of estrogens against coronary atherosclerosis and examine whether these effects are negated or modified by progestins, as well as whether adequate protection requires addition of statins and antioxidants.

R01 HL034594	Risk Factors for Cardiovascular Disease in Women	Manson	Brigham & Women's Hospital

Continued follow-up of the Nurses Health Study cohort, first recruited in 1976, to evaluate hypotheses regarding dietary and hormonal risk factors for coronary heart disease and ischemic and hemorrhagic stroke.

P01 HL045666	Cardiovascular Benefits of Soy Phytoestrogens	Kaplan	Wake Forest U.

A group of studies focused on the potential cardiovascular benefits of soy photoestrogen supplementation/treatment

P50 HL063494	SCOR in Ischemic Heart Disease: Cardiac Estrogen Receptors & MI	Mendelson	New Engl. Med. Ctr.

An investigation of the hypothesis that the genetics, expression, and function of cardiovascular estrogen receptors and estrogen-regulated target genes mediate protection against ischemic diseases and their sequelae, including vascular dysfunction, post-myocardial infarction remodeling, and arrhythmias.

R01 HL067128	Longitudinal Study of the Menopause and Fat Patterning	Powell	Rush Presbyterian-St. Luke's Med. Ctr.

A study of the natural history of the accumulation of intra-abdominal fat as women progress through menopause.

R01 HL068639	Hormone Replacement Therapy and Prothrombotic Variants	Psaty	U. Washington

An assessment of the interaction between hormone therapy and other procoagulant variants as it affects the risk of cardiovascular events.

F32 HL069648	Estrogen and Sympathetically Mediated Vasoconstriction	Fadel	U. Texas Southwest Medical Center

An examination of the influence of estrogen on the regulation of sympathetic vasocontstriction in contracting skeletal muscle to determine the mechanisms by which estrogen may confer vascular protection.

R01 HL073108	Reproductive Hormones and Pre-Clinical CVD in Women	Bairey Merz	Cedars-Sinai Medical Center

A study of the role of reproductive hormones in the progression of pre-clinical cardiovascular disease in pre-, peri-, and post-menopausal women.

R01 HL073410	Clotting Genetic Variant, Hormones, and Venous Thrombosis	Smith	U. Washington

A study to identify genetic variants in 12 key clotting proteins that may modify the risk of venous thromboembolism either independently, through gene-gene interactions, or in the presence of hormone use.

R01 HL074729	Postmenopause CHD Risk: Platelet Genes and Hormone Therapy	Bray	Baylor College of Medicine

A substudy of the WHI observational study exploring inherited platelet variants and their interactions with hormone therapy to identify genetic predictors of coronary heart disease events in women.

Multiproject	Prevalence & Progression of Subclinical Atherosclerosis

A determination of the extent to which diminishing ovarian function affects vascular function and accelerates the development of atherosclerosis in the coronary arteries, aorta, and carotid arteries.

Representative FY 2004 Publications

1. Bittner, V et al. Remnant-like lipoproteins, hormone therapy, and angiographic and clinical outcomes: the Women's Angiographic Vitamin and Estrogen Trial. Am Heart J 2004 Aug;148(2):293-99.

2. Wildman, RP et al. A dietary and exercise intervention slows menopause-associated progression of subclinical atherosclerosis as measured by intima-media thickness of the carotid arteries. J Am Coll Cardiol 2004 Aug 4;44(3):579-85.

3. Howard, BV et al. Postmenopausal hormone therapy is associated with atherosclerosis progression in women with abnormal glucose tolerance. Circulation 2004 Jul 13;110(2):201-06.

4. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004 Apr 14;291(14):1701-1712.

5. Olson, MB et al. Hormone replacement, race, and psychological health in women: a report from the NHLBI-sponsored WISE study. J Womens Health 2004 April;13(3):325-32.

6. Brownley, KA et al. Cardiovascular effects of 6 months of hormone replacement therapy versus placebo: differences associated with years since menopause. Am J Obstet Gynecol 2004 Apr;190(4):1052-58.

7. Chlebowski, RT et al. Estrogen plus progestin and colorectal cancer in postmenopausal women. N Engl J Med 2004 Mar 4;350(10):991-1004.

8. Zhang, Y et al. Associations of postmenopausal hormone therapy with markers of hemostasis and inflammation and lipid profiles in diabetic and nondiabetic American Indian women: the Strong Heart Study. J Womens Health 2004 Mar;13(2):155-63.

9. Waters DD et al. Women's Ischemic Syndrome Evaluation: current status and future research directions: report of the National Heart, Lung, and Blood Institute workshop. Circulation 2004 Feb 17;109(6):e53-55.

10. Hsia J et al. Estrogen plus progestin and the risk of peripheral arterial disease: the Women's Health Initiative. Circulation 2004 Feb 10;109(5):620-26.

11. Hersh, AL et al. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. JAMA 2004 Jan 7;291(1):47-53.

12. Girdler SS et al. Transdermal versus oral estrogen therapy in postmenopausal smokers: hemodynamic and endothelial effects. Obstet Gynecol 2004 Jan;103(1):169-80.

13. Simkin-Silverman LR et al. Lifestyle intervention can prevent weight gain during menopause: results from a 5-year randomized clinical trial. Ann Behav Med 2003 Dec;26(3):212-220.

14. Anderson, GL et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. JAMA 2003 Oct 1;290(13):1739-48.

15. Cauley, JA et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA 2003 Oct 1;290(13):1729-38.

16. Farag, NH et al. Autonomic responses to psychological stress: the influence of menopausal status. Ann Behav Med 2003 Oct;26(2):134-38.

Public Education

- The *Postmenopausal Hormone Therapy Fact Sheet* explains research findings, issues related to long- and short-term hormone use, risk factors for heart disease, and alternatives to hormone therapy. For a copy, visit www.nhlbi.nih.gov/health/women/pht_facts.htm.

- *The Heart Truth*, a national awareness campaign, targets women ages 40 to 60 and encourages them to take their heart health seriously, talk to their doctors about it, and take steps to reduce their risk. For more information, visit the campaign's Web site at www.nhlbi.nih.gov/health/hearttruth.

National

Institute on

Aging

(NIA)

NIA FY 2003-2004 Science Advances and Key Activities on Menopause

Advances

Decreased sensitivity to estrogen may help explain menopausal changes. A new study suggests that age-related changes in how the brain responds to the female sex hormone estrogen may be involved in a woman's transition through menopause. The study provides new clues about hormonal influences on hot flashes and night sweats experienced by some women in the menopause transition.

A new rodent model of the menopause. Traditionally, researchers have removed the ovaries in rodent models in order to explore biologic processes underlying the associations between "menopause" and pathophysiology of tissues and organs associated with postmenopausal health problems, such as osteoporosis and cardiovascular disease. However, NIA- supported investigators have recently developed a new model in which the animal retains its ovaries while accelerating loss of ovarian follicles, leaving the hypothalamic-pituitary-ovarian axis (the interdependent relationship between the ovaries and brain that regulates hormonal events such as menstruation) intact. This provides a new means to study the impact of follicle loss on the pathophysiology of various postmenopausal health problems and conditions.

Possible new mechanism for hot flashes. Although some 80 percent of women approaching menopause experience hot flashes, the symptoms' physiological trigger has yet to be identified. Results of a recent study of menopausal women suggest that conditions of fasting and low blood glucose may be factors the increase the likelihood of hot flashes. Interventions aimed at maintaining blood glucose may show promise in reducing the burden of hot flashes.

Women who experience premenstrual syndrome (PMS) are more likely to experience menopause-related symptoms. Although the PMS improves during the menopausal transition, investigators recently found that women who reported PMS when they were premenopausal are at greater risk of menopausal hot flushes, depressed mood, poor sleep, and decreased libido.

The menopause transition and depression. The role of the transition through the menopause and altered levels of reproductive hormone levels on depressed mood is controversial. To evaluate the role of changes in menopausal status and reproductive hormones levels on depressed mood, assessments were conducted in a sample of African American and white women. Researchers found that depressive symptoms increased during the menopause transition but decreased thereafter in postmenopausal women. The association of depressive symptoms with changes in reproductive hormones supports the hypothesis that the changing hormonal milieu contributes to disturbances in mood during transition to menopause.

Regular physical activity during the menopause transition can counter age-related weight gain. During the transition from premenopause to postmenopause, many women experience loss of lean mass and gains in weight, fat mass, and central fat deposition. However controversy exists regarding the degree to which the increases in total fat and central fat over the course of the menopausal transition are the result of menopause itself or a consequence of chronologic aging. To address this question, the investigators examined the potential role of aging, menopausal status, and physical activity on weight and waist circumference in 3,064 racially/ethnically diverse women aged 42-52 years at baseline who were participating in the Study of Women's Health Across the Nation (SWAN). Self-reported physical activity in various domains, including sports/exercise, household/caregiving and daily routine (defined as walking or biking for transportation) was assessed. Their findings suggest that, although midlife women tend to experience increases in weight and waist circumference over time, maintaining or increasing participation in regular physical activity can contribute to prevention or moderation of those gains. [Co-funded by OWRH]

Reproductive hormone levels vary markedly by race/ethnicity, body mass and stage of the menopause transition as women age. The menopausal transition is characterized by a progressive rise in serum follicle stimulating hormone (FSH) associated with a decrease in serum estradiol (E2) levels. In the first study of cross-sectional ethnic differences in levels of reproductive hormones in midlife women, investigators assayed E2 and FSH levels in the early follicular phase of a spontaneous menstrual cycle in three consecutive annual visits during the SWAN study. They found that:

- Serum E2 concentrations decreased significantly with age, with a steeper decline at higher ages.
- FSH concentrations increased significantly with age, with a steeper increase at higher ages.
- Similar patterns in the decline of E2 and the increase in FSH with age were found across ethnic groups, but the levels of these hormones differed by race/ethnicity.
- Over time, Chinese and Japanese women had lower E2 concentrations but similar FSH levels, compared to Caucasian women.
- African American women had higher FSH concentrations but comparable E2 levels with those of Caucasian women.
- These ethnic differences in E2 and FSH were independent of menopausal status (i.e., whether the woman was pre-or perimenopausal).
- Increasing body mass index (BMI) was associated with decreasing concentrations of E2 among premenopausal and early perimenopausal women but was associated with increasing concentrations of E2 among late perimenopausal and postmenopausal women.
- Increasing BMI was also associated with decreasing concentrations of FSH, with the effect of BMI becoming larger as women transitioned through menopause.

Ethnic differences in the relationships between E2 and FSH over time suggest the role of race/ethnicity as a potentially important determinant of changing pituitary-ovarian relationships between E2 and FSH with aging. These findings also underscore the importance of BMI as a determinant of hormone levels and raise the possibility that ethnic differences in menopausal symptoms and health outcomes may be related, at least in part, to ethnic differences in reproductive hormones and/or their interrelationships. [Co-funded by OWRH]

Memory loss is not an inherent outcome of the menopause transition. Previous studies have found increased self-reporting of forgetfulness during the menopausal transition. These findings have been consistent with the widespread belief that the hormonal changes culminating in, or due to, the menopause produce predominantly deleterious global changes in health status and/or accelerate the aging process(es). However, investigators on the Study of Women's Health Across the Nation, a study of the menopausal transition, observed small but significant improvements in cognitive scores with aging after adjusting for ethnicity, education, income and self-reported health. Significant improvements in working memory and perceptual speed were observed from pre-menopause through later stages of menopause. In women who became post-menopausal, working memory improved but perceptual speed declined. Although additional follow-up is needed, many will find the results of the study reassuring, in that they provide no evidence for a menopause-related decline in mental function that had been suggested based on earlier studies. [Co-funded by ORWH]

Activities

January 20, 2004: Workshop on Assessing and Improving Measures of Hot Flashes. NIA participated in this workshop, which was convened by NCCAM, in collaboration with the Office of Research on Women's Health (ORWH), NIBIB, NCI, NHLBI, NICHD, the Office of Extramural Research (OER), and the Office of Behavioral and Social Sciences Research (OBSSR). The objectives of this workshop included assessing our understanding of the physiological and endocrine parameters associated with hot flashes, the self-reported experience of hot flashes, and the quality of existing

subjective and objective measures of hot flashes, and the barriers and opportunities to improve these measures.

May 26-27, 2004: The Biology of the Perimenopause: Impact on Health and Aging. The 1.5 day workshop consisted of 4 plenary lectures (Premenopausal protection against chronic diseases of aging: rethinking the paradigms; Neurobiology of ovarian steroids; Dynamics of the female reproductive system and changes with aging; Relating aging and outcomes of menopause) and 6 broader discussion sessions (animal models, adipose tissue, immune system, bone, cardiovascular, and cognition and brain function). The presentations and discussion explored the hypothesis that changes in hypothalamic-pituitary-ovarian (H-P-O) axis hormones (estrogen, androgen, progesterone, inhibin/activin, gonadotropins, etc.) and hormonal dynamics across the menopausal transition in middle-aged women increase the risk for disease and other pathophysiologic conditions in non-reproductive end organs and systems. Co-funded by ORWH.

September 28-29, 2004: Bench to Bedside: Estrogen as a Case Study. While the majority of studies published to date in animal models indicate that estrogen's effects are beneficial, clinical studies have provided inconsistent results. This workshop was held to examine the reasons why basic science, epidemiological, and some clinical studies have had different outcomes than clinical trials. The workshop had four objectives:

- To define and examine the discrepancies between the findings of the Women's Health Initiative (WHI)/ Women's Health Initiative Memory Study (WHIMS) on brain and cognitive function and the basic and longitudinal/epidemiological studies
- To examine the effects of estrogens on brain and cognitive function as they relate to aging
- To determine what is known and what information we would need to obtain that would determine whether additional hormone "interventions" could be developed
- To determine what lessons we have learned from studies on estrogen that will help in designing clinical trials for other classes of drugs.

An RFA, "Biology of the Perimenopause: Impact on Health and Aging," has been released and will be funded in 2006. The goal of this RFA is solicit applications for research studies to better understand underlying biologic mechanisms associated with the increased risk for, or decreased protection leading to, health problems and conditions associated with the menopausal process in middle-aged women.

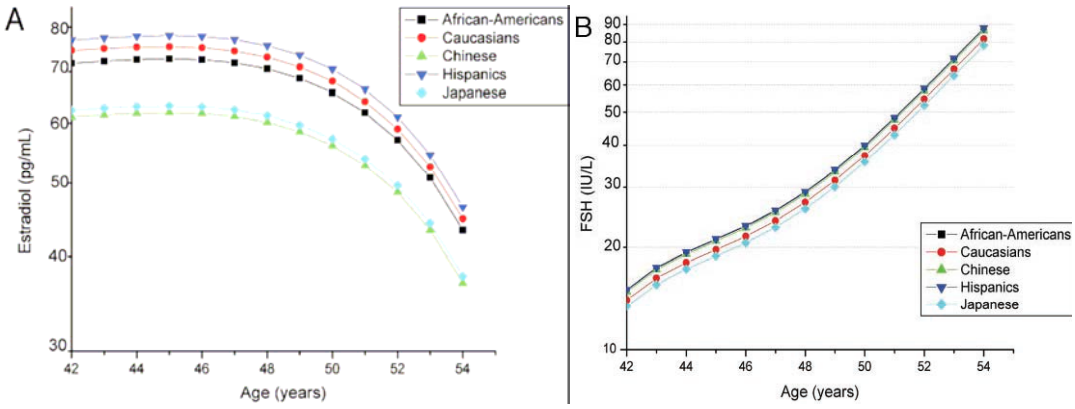
NIA is collaborating with the National Center for Complementary and Alternative Medicine on a clinical trial called "Does Menopause Matter?" The purpose of this study is to follow a woman's progression through menopause in order to examine the effects on health-related quality of life and use of health care resources, and to understand how women are using alternative therapies. Recruitment has not yet begun, but ultimately 720 women are expected to participate.

Research Advance(s)

Reproductive hormone levels vary markedly by race/ethnicity, body mass and stage of the menopause transition as women age. The transition from active reproductive potential to reproductive senescence in women is characterized by a progressive rise in serum follicle stimulating hormone (FSH) associated with a decrease in serum estradiol (E2) levels. However, no study has investigated cross-sectional ethnic differences in levels of reproductive hormones in midlife women, let alone longitudinal changes associated with the menopause transition. In order to determine whether there are differences in hormones that can be explained by host factors, E2 and FSH were assayed in serum collected primarily in the early follicular phase of a spontaneous menstrual cycle in three consecutive annual visits. At the baseline visit, 46.2% of the women were classified as being early perimenopausal, with the remaining being premenopausal. By the second follow-up visit, 5.5% of the women in that cohort were postmenopausal, 66.8% were early perimenopausal, 8.3% were late perimenopausal, and 19.4% remained premenopausal. Serum E2 concentrations decreased significantly with age (figure A), with a steeper decline at higher ages. FSH concentrations increased significantly with age (figure B), with a steeper increase at higher ages. Similar patterns in the decline of E2 and the increase in FSH with age were found across ethnic groups, but the levels of these hormones differed by race/ethnicity. Specifically, over time, Chinese and Japanese women had lower E2 concentrations but similar FSH levels, compared to Caucasian women, whereas African American women had higher FSH concentrations but comparable E2 levels with those of Caucasian women.

These ethnic differences in E2 and FSH were independent of menopausal status. Interestingly, the effect of body mass index (BMI) on serum E2 and FSH levels varied by menopausal status. Increasing BMI was associated with decreasing concentrations of E2 among premenopausal and early perimenopausal women but was associated with increasing concentrations of E2 among late perimenopausal and postmenopausal women. Increasing BMI was also associated with decreasing concentrations of FSH, with the effect of BMI becoming larger as women transitioned through menopause.

Ethnic differences in the relationships between E2 and FSH over time suggest the role of race/ethnicity as a potentially important determinant of changing pituitary-ovarian relationships between E2 and FSH with aging. These findings also underscore the importance of BMI as a determinant of hormone levels and raise the possibility that ethnic differences in menopausal symptoms and health outcomes may be related, at least in part, to ethnic differences in reproductive hormones and/or their interrelationships. [**The SWAN Investigators**; UO1 AG12505; UO1 AG12535;U01 NR0406; U01 AG12531, UO1 AG12539, U01 AG12546, U01 AG12553, U01 AG12554, UO1 AG12495]



Randolph JF Jr, Sowers M, Bondarenko IV, Harlow SD, Luborsky JL, Little RJ. Change in estradiol and follicle-stimulating hormone across the early menopausal transition: effects of ethnicity and age. J Clin Endocrinol Metab. 2004;89(4):1555-61.

Regular physical activity during the menopause transition can counter age-related weight gain. During the transition from premenopause to postmenopause, many women experience loss of lean mass and gains in weight, fat mass, and central fat deposition. However controversy exists regarding the degree to which the increases in total fat and central fat over the course of the menopausal transition are the result of menopause itself or a consequence of chronologic aging. To address this question, the investigators examined the potential role of aging, menopausal status, and physical activity on weight and waist circumference in 3,064 racially/ethnically diverse women aged 42-52 years at baseline who were participating in the Study of Women's Health Across the Nation (SWAN), an observational study of the menopausal transition. Self-reported physical activity in various domains, including sports/exercise, household/caregiving and daily routine (defined as walking or biking for transportation) was assessed. Over 3 years of follow-up, mean weight increased by 2.1 kg or 3.0% and mean waist circumference increased by 2.2 cm or 2.8%. However, changes in menopausal status were not significantly associated with weight gain or with increases in waist circumference. Importantly, a one-unit increase in reported level of sports/exercise (on a scale of 1-5) was related to a highly significantly decrease of 0.32 kg in weight and an absence of increases in waist circumference. Weight and waist circumference changes were likewise related to changes in daily routine physical activity (biking and walking for transportation and less television viewing). These findings suggest that, although midlife women tend to experience increases in weight and waist circumference over time, maintaining or increasing participation in regular physical activity can contribute to prevention or moderation of those gains. [**The SWAN Investigators**; UO1 AG12505; UO1 AG12535;U01 NR0406; U01 AG12531, UO1 AG12539, U01 AG12546, U01 AG12553, U01 AG12554, UO1 AG12495]

Sternfeld B, Wang H, Quesenberry CP Jr, Abrams B, Everson-Rose SA, Greendale GA,et al. Physical activity and changes in weight and waist circumference in midlife women: findings from the Study of Women's Health Across the Nation. Am J Epidemiol. 2004;160(9):912-22.

The menopause transition and depression. The role of the transition through the menopause and altered levels of reproductive hormone levels on depressed mood is controversial. To evaluate the role of changes in menopausal status and reproductive hormones levels on depressed mood, assessments were conducted in a randomly identified, population-based, sample of 218 African American and 218 white women aged 35 to 47 years with regular menstrual cycles and no hormonal or psychotropic medication use. There were six assessment periods and 12 blood draws during a 4-year study interval of these midlife women participants in the Penn Ovarian Aging Study.

After adjustment for other predictors of depression (history of depression, severe premenstrual syndrome, poor sleep, age, race, and employment status), there was an increased likelihood of depressive symptoms during the menopause transition and a decreased likelihood after menopause. The likelihood of depressive symptoms decreased for individuals with a rapidly increasing follicle-stimulating hormone (FSH) profile and also decreased with age compared

with premenopausal women. It was also observed that women with increasing estrogen profiles (which occur during the early transition to menopause)reported more depressive symptoms. It was concluded that the depressive symptoms assessed in this study increased during the menopause transition but decreased thereafter in postmenopausal women. The association of depressieve symptoms with changes in reproductive hormones supports the hypothesis that the changing hormonal milieu contributes to dysphoric (disturbances in) mood during transition to menopause. [E. Freeman, U Pennsylvania, Philadelphia; R01 AG12745]

Freeman EW, Sammel MD, Liu L, Gracia CR, Nelson DB, Hollander L. Hormones and menopausal status as predictors of depression in women in transition to menopause. Arch Gen Psychiatry. 2004;61(1):62-70.

Title: Decreased Sensitivity in the Brain to Estrogen May Help Explain Menopausal Changes

Background: There is a marked decline in estrogen (E) levels after the final menstrual cycle and the start of the postmenopausal period. However, earlier, in their forties, as women enter the menopause transition and approach their final menstrual period (FMP), changes in menstrual cycle regularity and hormonal patterns occur as does an increase in the reporting of symptoms such as hot flashes and night sweats. The NIH-supported Study of Women's Health Across the Nation (SWAN), a multi-site survey of 3300 women who were 42-52 years of age when they were enrolled in the study in 1996 follows the biological, physical and hormonal changes experienced by women as they approach and traverse the menopause transition.

Advance: In a substudy that involved the daily collection of urine samples and questionnaire data about symptoms, different patterns of hormone fluctuations were observed in women who did not ovulate. In one group of women, there was a surge of luteinizing hormone (LH), an appropriate response to the rise in E levels occurring in early part of the menstrual cycle. In the second, the same increases in E were not associated with an LH surge. In the third group, although E levels in the early part of the cycle were similar to levels in groups 1 and 2, E levels did not show similar increases as the cycle progressed, there was no LH surge and LH levels were higher for most of the cycle. The hormonal patterns in groups 2 and 3 suggest different kinds of reduced sensitivity of estrogen in the brain. Interestingly, the women in the third group had significantly more hot flashes and night sweats than those in the other two groups.

Implications: These findings 1) suggest that a specific hormonal pattern linked to increased hot flashes reflects alterations in the sensitivity of the brain to estrogen and 2) provide new clues about hormone influences on hot flashes and night sweats as women approach menopause. A better understanding of the role of changing levels of, and responses to, hormones such as E and LH in causing menopause-related symptoms is needed to develop new approaches for managing symptoms occurring during the menopause transition.

Citation:

Weiss G, Skurnick JH, Goldsmith LT, Santoro NF, Park SJ. Menopause and hypothalamic-pituitary sensitivity to estrogen. JAMA. 2004 Dec 22;292(24):2991-6

Decreased sensitivity in the brain to estrogen may help explain menopausal changes (Public release date: 21-Dec-2004)

A new study suggests that age–related changes in how the brain responds to the female sex hormone estrogen may be involved in a woman's transition through menopause. The study provides new clues about hormonal influences on hot flashes and night sweats experienced by some women in the menopause transition.

The findings are reported in the December 22/29, 2004, Journal of the American Medical Association* and are based on data from the Study of Women's Health Across the Nation (SWAN), a multi-site survey of women going through the menopause transition. This study is funded by the National Institutes of Health.

"Throughout a woman's reproductive life, there are not only age-related changes in estrogen levels, but also differences in how her body responds to given levels of estrogen. Researchers have been trying to understand how and why these changes take place," says Sherry Sherman, Ph.D., project director of the SWAN study, National Institute on Aging (NIA). "Hormone patterns found in this study could mean that, with age, a part of a woman's brain which regulates reproductive hormone levels may become less sensitive to estrogen. Other study findings suggest that the decreases in sensitivity can lead to significantly increased hot flashes and night sweats."
The analysis was led by Gerson Weiss, M.D., New Jersey Medical School at the University of Medicine and Dentistry of New Jersey (UMDNJ), who with his colleagues from the SWAN study reported the findings. UMDNJ is one of seven SWAN sites supported by the NIA, the National Institute of Nursing Research, and the Office of Research on Women's Health, all parts of the National Institutes of Health (NIH) at the Department of Health and Human Services.
SWAN follows more than 3,300 women, ages 42-52 at the beginning of the study in 1995, as they experience the changes associated with approaching menopause. The data for this report came from the Daily Hormone Study, a substudy that involves the daily collection of urine samples and completion of a questionnaire about symptoms, for a period of one menstrual cycle or a maximum of 50 days (if no menstruation occurs).

Through this sampling, the study characterized the fluctuations in hormones such as estrogen, which is produced by the ovary, and fluctuations in other hormones such as luteinizing hormone (LH), which is produced by the pituitary, a gland at the base of the brain. These reproductive hormones are needed for normal menstrual cycles and to prepare the body for pregnancy.
In this study, the hormone levels in some of these middle-aged women reflected a likely insensitivity to estrogen in the brain. The data showed three different patterns of hormone fluctuations in women who did not ovulate: the first group of women had a surge of LH--an "appropriate" response to increases in estrogen. In a second group, the same increases in estrogen were not associated with a surge in LH. In the third group, estrogen levels early in the cycle were similar to those of groups 1 and 2, but, unlike those two groups, did not show further increases. The LH levels in this group did not show a surge and were higher for most of the cycle than in the other groups. The hormonal patterns in groups 2 and 3 suggest different kinds of reduced sensitivity to estrogen (or abnormal estrogen "feedback") in the brain.
Interestingly, the women in the third group had significantly more hot flashes and night sweats than women in the other two groups. These findings suggest that the hormonal pattern associated

with increases in symptoms reflects alterations in the sensitivity to estrogen in the brain. Additional follow-up of the women as they experience their final menstrual period and become postmenopausal is needed to further clarify the hormonal changes underlying the menopause transition as well as those causing hot flashes.

The findings in these women are the first to describe hormone patterns reflecting changes in responses to estrogen and are consistent with previous studies in other mammals that have described similar central nervous system insensitivity to estrogen with aging. A better understanding of the role of changing responses to reproductive hormones including estrogen in causing menopause-related symptoms is needed to develop new approaches for managing symptoms occurring at this time.

Because of the need to identify treatment options for women experiencing symptoms such as hot flashes during the menopause transition, the NIA and NIH's Office of Medical Applications of Research are sponsoring a State-of-the Science Conference on Management of Menopause-Related Symptoms, March 21-23, 2005, in Bethesda, MD. This meeting will bring together experts in the field who will present information on the biology of the menopause transition, common symptoms during this time, and possible treatments to an independent panel. This panel will prepare a state-of-the-science statement to provide guidance to women and their doctors, as well as to suggest future research directions.

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Further information is available at www.consensus.nih.gov.
The NIA, www.nia.nih.gov, conducts and supports research on aging and age-related diseases. For more information on menopause, please visit the NIH's Menopausal Hormone Therapy page at http://www.nih.gov/PHTindex.htm. To request a free copy of the NIA brochure, Menopause: One Woman's Story, Every Woman's Story, visit www.niapublications.org, or call 1-800-222-2225. The National Institute of Nursing Research, http://ninr.nih.gov, supports clinical and basic research in order to provide a scientific basis for the care of individuals across the lifespan. The Office of Research on Women's Health, http://www4.od.nih.gov/orwh/, works to advance research activities on behalf of all women.

*Weiss, G, Skurnick, JH, Goldsmith, LT, Santoro, NF, and Park, SJ, Menopause and Hypothalamic-Pituitary Sensitivity to Estrogen. JAMA. 2004.

Grant Number	PI Name	Project Title
Menopause		
1K23AG024254-01	HESS, RACHEL	Does Menopause Matter?
1R01AG024154-01	HODIS, HOWARD	Biologic Response of Menopausal Women to 17B-Estradiol
5R01AG021948-02	HOYER, PATRICIA	Ovary Intact Murine Model for Menopause
5R01AG014124-08	YOUNG, TERRY	Menopause and Midlife Aging Effects on Sleep Disorders
5R01AG019361-03	GOLD, ELLEN	Sleep during the peri-menopause in a multi-ethnic cohort
5R01AG013204-08	VOYTKO, MARY LOU	Cognition and Estrogen in Menopause:A Monkey Model
5R01AG012745-09	FREEMAN, ELLEN	EPIDEMIOLOGIC STUDY OF THE LATE REPRODUCTIVE YEARS

5R01AG019362-03	HALL, MARTICA	Sleep During the Perimenopause in a Multi-Ethnic Cohort
5R01AG021543-02	HARLOW, SIOBAN	Staging Reproductive Aging in Five Cohort Studies
5R01AG019363-03	KRAVITZ, HOWARD	Sleep During the Perimenopause in a Multi-Ethnic Cohort
1Z01AG000293-15	METTER, EARL	Biochemical Parameters Of Bone Metabolism Age
5R01AG020162-02	MOORMAN, PATRICIA	Ovarian Failure Among Hysterectomized Women
5R01AG009214-12	RANCE, NAOMI	Reproductive Aging and the Human Hypothalamus
5R01AG019360-03	SOWERS, MARYFRAN	Sleep During the Perimenopause in a Multi-Ethnic Cohort
5R37AG021665-02	SOWERS, MARYFRAN	Estrogen, Metabolism, Menopause, and Health Outcomes
2U01AG012531-11A1	FINKELSTEIN, JOEL	Study of Women's Health Across the Nation - III
2U01AG012554-11A1	GOLD, ELLEN	Study of Women's Health Across the Nation III--UC Davis
5R01AG018408-05	GOLDBERG, ANDREW	MENOPAUSE, LPL GENOTYPE AND METABOLISM AFTER WEIGHT LOSS
5R01AG018198-05	KOHRT, WENDY	MODULATION OF VISCERAL FAT BY ESTROGENS AFTER MENOPAUSE
2U01AG012546-11A1	MATTHEWS, KAREN	Womens Health Across the Nation
2U01AG012495-11A1	MCCONNELL, DANIEL	Study of Women's Health Across the Nation-Endocrine Lab
5R01AG017057-04	NEWTON, KATHERINE	ALTERNATIVE THERAPIES FOR MENOPAUSE: A RANDOMIZED TRIAL
5R01AG017104-05	SOWERS, MARYFRAN	FUNCTIONAL STATUS AND THE MENOPAUSAL TRANSITION
5R01AG020082-03	VITIELLO, MICHAEL	PROGESTERONE AND SLEEP IN OLDER WOMEN
5R01AG015857-05	CHAUDHURI, GAUTAM	ROLE OF NO AND ESTRADIOL IN AGING AND ATHEROGENESIS
1R03AG023251-01A1	DEMERATH, ELLEN	Telomere Length as a Marker of Cardiovascular Aging
2U01AG012539-11A1	GREENDALE, GAIL	Study of Woman's Health Across the Nation - UCLA
1R01AG023139-01A1	KUEHL-KOVARIK, MARY	Functional changes in GnRH neurons with age
1Z01AG000647-07	NAGARAJA, RAMAIAH	Genes Assoc With Ovarian Develop /Premature Ovarian Fail
5R01AG021476-02	NEWHOUSE, PAUL	Estrogen Effects on Cholinergic Function in Older Women
5R01AG017578-05	OBERMEYER, CARLA	THERAPEUTIC DECISIONS AT MENOPAUSE--A MULTISITE STUDY
2U01AG012505-11A1	POWELL, LYNDA	Study of Women's Health Across the Nation
2P01AG004875-210001	RIGGS, B. LAWRENCE	PATHOPHYSIOLOGY OF OSTEOPOROSIS IN AGING WOMEN
2U01AG012535-11A1	SANTORO, NANETTE	SWAN-Study of Women's Health Across the Nation-N.J.site

1R03AG023330-01	SINGH, MEHARVAN	Progesterone, GABA Receptors and Cell Survival
5U01AG017719-05	SOWERS, MARYFRAN	SWAN REPOSITORY
2U01AG012553-10A1	TYRRELL, KIM	Study/Women/Health Across Nation III/Coordinating Center
5K01AG019630-03	VAN PELT, RACHAEL	ESTROGEN, INSULIN AND REGIONAL LIPOLYSIS IN OLDER WOMEN
5U01AG021382-03	ZELINSKI-WOOTEN, MARY	Ovarian Aspects of Caloric Restriction
5R01AG021593-02	AVIV, ABRAHAM	Telomeres and Vascular Aging
1R03AG023925-01	BIMONTE-NELSON, HEATHER	Progesterone, aging, and memory loss
5K12AG019247-03	CARNES, MARY	WOMEN'S HEALTH AND AGING: CLINICAL SCIENTIST DEVELOPMENT
1F32AG023430-01A1	DUMAS, JULIE	Estrogen and Cognition In Postmenopausal Women
5R01AG017170-06	ELLIOT, SHARON	Estrogen Deficiency and REnal Disease in Aging Women
5R01AG018400-04	FLAWS, JODI	Risk Factors for Hot Flashes in Mid-Life
5R37AG005233-17	FREEDMAN, ROBERT	BEHAVIORAL TREATMENT OF MENOPAUSAL HOT FLASHES
5R01AG020116-02	GOLDBERG, ANDREW	Race, Lipoprotein Lipase and Obesity after Menopause
5R01AG015955-06	GORODESKI, GEORGE	Estrogen and Aging effects on Transvaginal Transpoet
5R01AG013241-06	HALL, JANET	Aging and the Hypothalamic-Pituitary Reproductive Axis
5R01AG018798-04	HODIS, HOWARD	ESTROGEN IN THE PREVENTION OF ATHEROSCLEROSIS TRIAL
5R01AG015345-07	INSOGNA, KARL	Role of IL-6 in PTH-Induced Bone Resorption
3R01AG018198-05S1	KOHRT, WENDY	MODULATION OF VISCERAL FAT BY ESTROGENS AFTER MENOPAUSE
2P01AG004875-210002	MELTON, L. JOSEPH III%	RISK FACTORS FOR HIP FRACTURES AMONG THE ELDERLY
5R01AG020583-03	NICKLAS, BARBARA	Excercise and Regional Fat Metabolism after Menopause
3R01AG020583-03S1	NICKLAS, BARBARA	Excercise and Regional Fat Metabolism after Menopause
5R01AG020263-03	RICKLEFS, ROBERT	Demographic Aging in Captive Birds and Mammals
1T32AG023475-01	ROSSETTI, LUCIANO	Training in Aging Research
3R01AG013204-07S1	VOYTKO, MARY LOU	Cognition and Estrogen in Menopause:A Monkey Model
5P01AG017164-05	WISE, PHYLLIS	FEMALE REPRODUCTIVE AGING: THE ROLE OF ESTROGEN
Aging Women		
2T32AG000265-06	CARNES, MARY	Women's Health & Aging:Research and Leadership Training

5R01AG013241-06	HALL, JANET	Aging and the Hypothalamic-Pituitary Reproductive Axis
5R01AG021543-02	HARLOW, SIOBAN	Staging Reproductive Aging in Five Cohort Studies
5R01AG017042-05	ANVERSA, PIERO	AGE, GENDER AND THE FAILING HEART
5R37AG019905-04	FRIED, LINDA	Pathogenesis of physical disability in Aging women
1Z01AG000191-08	RESNICK, SUSAN	Neuroimaging Predictors Of Cognitive Change And Response
5K23AG019161-03	CAPPOLA, ANNE	Androgens, Myostatin, and Sarcopenia in Older Women
5K12AG019247-03	CARNES, MARY	WOMEN'S HEALTH AND AGING: CLINICAL SCIENTIST DEVELOPMENT
5R01AG017170-06	ELLIOT, SHARON	Estrogen Deficiency and REnal Disease in Aging Women
5R01AG012745-09	FREEMAN, ELLEN	EPIDEMIOLOGIC STUDY OF THE LATE REPRODUCTIVE YEARS
5U01AG020487-04	HOLLOSZY, JOHN	Caloric Restriction and Aging in Humans
5R01AG018843-02	JANOWSKY, JERI	Mechanisms for sex steroid effects on cognition in aging
5P01AG018911	CACIOPPO, JOHN	Social Isolation, Loneliness, Health, and Aging Women
2P01AG004875-21	KHOSLA, SUNDEEP	Physiology of Bone Metabolism in an Aging Population
1Z01AG000908-04	LING, SHARI	Inflammation and Osteoarthritis of the Knee
2U01AG012495-11A1	MCCONNELL, DANIEL	Study of Women's Health Across the Nation-Endocrine Lab
1Z01AG000802-13	NAJJAR, SAMER	Effects Of Age And Conditioning Status On Rest And Exerc
2P01AG004875-210001	RIGGS, B. LAWRENCE%	PATHOPHYSIOLOGY OF OSTEOPOROSIS IN AGING WOMEN
5R01AG014799-08	VELDHUIS, JOHANNES	THE AGING GH AXIS IN POSTMENOPAUSAL WOMEN
5R01AG015857-05	CHAUDHURI, GAUTAM	ROLE OF NO AND ESTRADIOL IN AGING AND ATHEROGENESIS
5R01AG017496-05	DOTY, RICHARD	POSTMENOPAUSAL ESTROGEN INFLUENCES ON OLFACTION
5R01AG021106-02	FUKAGAWA, NAOMI	Age-related changes in glutathione synthesis
1Z01AG007360-01	GURALNIK, JACK	Single Nucelotide Polymorphisms and Disability
5R01AG007004-15	KENNEY, W.	AGE AND CONTROL OF HUMAN SKIN BLOOD-FLOW
2P01AG004875-210006	KHOSLA, SUNDEEP	PATHOPHYSIOLOGY OF OSTEOPOROSIS IN AGING MEN
1Z01AG000293-15	METTER, EARL	Biochemical Parameters Of Bone Metabolism--age And Sex C
1Z01AG000636-15	METTER, EARL	Study Of Physical Activities In The Blsa
5K01AG020683-03	MOREAU, KERRIE	HRT and Exercise Effects on Central Arterial Compliance
5R01AG021500-02	ROTH, STEPHEN	Genetic Architecture of Aging Skeletal Muscle
5R01AG018409-04	TRAPPE, SCOTT	Single Muscle Fiber Contractile Properties With Aging
5P01AG011412-090009	VAN CAUTER, EVE	"IMPACT OF A SLEEP DEBT IN MIDDLE-AGED AND OLDER ADULTS"

5R01AG021918-02	YAFFE, KRISTINE	Sex Hormones, Related Polymorphisms & Cognitive Decline
5R01AG014124-08	YOUNG, TERRY	Menopause and Midlife Aging Effects on Sleep Disorders
5R01AG017973-04	ADLER, SHELLEY	OLDER PATIENT-PHYSICIAN-ALTERNATIVE HEALER RELATIONSHIPS
5R01AG020521-02	BENZ, CHRISTOPHER	Biology of Breast Cancers Arising in Older Women
1R03AG023925-01	BIMONTE-NELSON, HEATHER	Progesterone, aging, and memory loss
5R01AG019825-03	CARLSON, MICHELLE	Cognitive Pathways to Disability
7U01AG018197-06	CUMMINGS, STEVEN	OSTEOPOROTIC FRACTURES IN MEN
5T32AG020506-03	DISTERHOFT, JOHN	Mechanisms of Aging and Dementia Training Program
5R01AG011703-11	FRIED, LINDA	RISK FACTORS FOR PHYSICAL DISABILITY IN AGING WOMEN
5R01AG017880-03	GREENBLATT, DAVID	CYP3A Function in Aging AfricanAmericans
1R01AG022551-01A1	GRIGSBY, JAMES	Chemotherapy & Cognition in Older breast Cancer Patients
1Z01AG007310-03	GURALNIK, JACK	Pain And Physical Functioning in Older Women
5R01AG018336-04	HURLEY, BERNARD	GENE EFFECTS ON STRENGTH RESPONSES TO AGE AND EXERCISE
1R03AG023860-01	KANG, JAE	Plasma Markers of Dietary Intervention to Delay Cogniti
5R01AG019327-04	KNOWLTON, ANNE	AGING, ESTROGEN, HSPS AND MYOCARDIAL ISCHEMIA
2U01AG012546-11A1	MATTHEWS, KAREN	Womens Health Across the Nation
5K08AG021631-02	NEUNER, JOAN	Adoption of osteoporosis screening in older women
5R01AG021476-02	NEWHOUSE, PAUL	Estrogen Effects on Cholinergic Function in Older Women
2U01AG012505-11A1	POWELL, LYNDA	Study of Women's Health Across the Nation
5R01AG009214-12	RANCE, NAOMI	Reproductive Aging and the Human Hypothalamus
5U01AG020480-03	ROBERTS, SUSAN	Dietary Energy Restriction and Metabolic Aging in Humans
2U01AG012535-11A1	SANTORO, NANETTE	SWAN-Study of Women's Health Across the Nation-N.J.site
5R01AG006537-18	SEALS, DOUGLAS	Age, Gender, Exercise & Autonomic-Physiological Function
1R01AG022241-01A1	SEALS, DOUGLAS	HRT, SERMs and LEG BLOOD FLOW IN POSTMENOPAUSAL WOMEN
1R03AG023330-01	SINGH, MEHARVAN	Progesterone, GABA Receptors and Cell Survival
5R03AG022062-02	STEVENS, JUNE	Obesity, diet and functional health in African-Americans
2U01AG012553-10A1	TYRRELL, KIM	Study/Women/Health Across Nation III/Coordinating Center
5P60AG017231-050002	URBAN, RANDALL	Androgens and nutrition in older Americans

5K01AG019630-03	VAN PELT, RACHAEL	ESTROGEN, INSULIN AND REGIONAL LIPOLYSIS IN OLDER WOMEN
5R01AG018339-05	VON MUHLEN, DENISE	DHEA REPLACEMENT IN HEALTHY OLDER MEN AND WOMEN
1R01AG022073-01A1	ALLEN, SUSAN	Unmet Need: An Acute/Chronic Care Link
5R01AG021203-03	ALWIN, DUANE	Latent Growth Curve Models of Cognitive Aging
5T32AG000208-14	ALWIN, DUANE	POPULATION STRUCTURE/HEALTH/BIOLOGY OVER THE LIFE COURSE
1Z01AG000600-16	ANDERSON, DAVID	Respiratory Factors In Blood Pressure Regulation
1R43AG024676-01	BEAUCHAMP, NATASHA	Multimedia Support for Caregivers of the Seriously Ill
5R01AG018760-04	BEHAN, MARY	Age,Gender, Serotonin and Respiratory Control
2R01AG007977-21A2	BENGTSON, VERN	A Longitudinal Study of Generations and Mental Health
5R37AG006945-18	BLAIR, STEVEN	Impact of Physical Fitness and Exercise on Health
1R01AG021493-01A2	BLAUM, CAROLINE	Hyperglycemia, Frailty and Disability in Older Women
5R01AG019147-04	BOOTH, SARAH	Effect of Vitamin K on Age-Related Bone Loss
1K23AG021605-01A1	CARLSSON, CYNTHIA	Effect of Statins on Pathobiology of Alzheimer's Disease
3T32AG000265-05S1	CARNES, MARY	WOMEN'S HEALTH AND AGING: RESEARCH & LEADERSHIP TRAINING
3T32AG000265-06S1	CARNES, MARY	Women's Health & Aging:Research and Leadership Training
1R01AG023802-01	COLTON, CAROL	Immune Responsiveness, APOE/Gender in Neurodegeneration
1Z01AG000183-16	COSTA, PAUL	Basic Research In Personality
1R03AG023301-01	DAVEY, ADAM	Multilevel Analysis of Formal & Informal Care in Sweden
1R03AG022671-01A1	DUDAS, STEVEN	Aging and Cancer of the Colon
1F32AG023430-01A1	DUMAS, JULIE	Estrogen and Cognition In Postmenopausal Women
5R01AG018695-04	DUNN, JULIE	Estrogen, Vitamin E, and Cognitive Change in Women
2R44AG019082-02	EAKER, ELAINE	Testing An Interactive website for Hormone Replacement
5R01AG022987-02	ENGELHARDT, GARY	Pension Wealth Calculators for Employer-Provided Plans
5R01AG005394-20	ENSRUD, KRISTINE	Study of Osteoporotic Fractures
1Z01AG000513-04	EVANS, MICHELE	Healthy Aging In Neighborhoods of Diversity Across Life
1Z01AG000730-09	EVANS, MICHELE	DNA Damage And Repair In Breast Cancer
1P01AG023591-010003	EVANS, WILLIAM	INSULIN RESISTANCE AND PROTEIN METABOLISM
5U01AG018820-04	FELSON, DAVID	MULTICENTER OSTEOARTHRITIS STUDY (MOST)
2U01AG012531-11A1	FINKELSTEIN, JOEL	Study of Women's Health Across the Nation - III
5K08AG020145-03	FITCHETT, GEORGE	The Role of Daily Spirituality in the Disease Process
5R01AG018400-04	FLAWS, JODI	Risk Factors for Hot Flashes in Mid-Life
3R37AG019905-04S1	FRIED, LINDA	Pathogenesis of physical disability in Aging women
3R37AG019905-04S2	FRIED, LINDA	Pathogenesis of physical disability in Aging women
5R01AG008825-12	FRIEDMAN, HOWARD	PREDICTORS OF HEALTH AND LONGEVITY
2P30AG017253-069002	GARBER, ALAN	CORE--EXTERNAL INNOVATIVE INTERNATIONAL NETWORK

1R03AG024647-01	GIEBULTOWICZ, JADWIGA	Longevity and reproduction in Drosophila
1R01AG025015-01	GLOWACKI, JULIE	Effect of Aging & Vitamin D Status on Osteoblastogenesis
2U01AG012554-11A1	GOLD, ELLEN	Study of Women's Health Across the Nation III--UC Davis
1R01AG021961-01A2	GOODPASTER, BRET	Skeletal Muscle Lipid and Insulin Resistance in Aging
5P60AG017231-05	GOODWIN, JAMES	UTMB CLAUDE PEPPER OLDER AMERICANS INDEPENDENCE CENTER
5R01AG015955-06	GORODESKI, GEORGE	Estrogen and Aging effects on Transvaginal Transpoet
1R01AG023096-01A1	GRAVEKAMP, CLAUDIA	DNA vaccines for metastatic breat cancer at old age
2U01AG012539-11A1	GREENDALE, GAIL	Study of Woman's Health Across the Nation - UCLA
2P50AG005134-21	GROWDON, JOHN	Massachusetts Alzheimer's Disease Research Center
5R01AG009775-12	HAUSER, ROBERT	The Wisconsin Longitudinal Study: As We Age
5F32AG021374-02	HAYS, NICHOLAS	Effect of diet on insulin sensitivity and energy balance
1P01AG024387-01	HELFERICH, WILLIAM	PHYTOESTROGENS AND AGING: DOSE, TIMING & TISSUE
1P01AG024387-010001	HELFERICH, WILLIAM	GENISTEIN INDUCES ENDOCRINE-RESISTANCE IN BREAST TUMORS
1K23AG024254-01	HESS, RACHEL	Does Menopause Matter?
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5R01AG011451-11	HOYER, WILLIAM	AGING OF COGNITIVE MECHANISMS
5R01AG015345-07	INSOGNA, KARL	Role of IL-6 in PTH-Induced Bone Resorption
5R01AG012611-10	JANOWSKY, JERI	The role of sex hormones on cognition
1K01AG021457-01A2	JOSEPH, LYNDON	Age, Lifestyle, Muscle Mechanisms in Insulin Resistance
5R01AG018887-04	KENNY, ANNE	TESTOSTERONE FOR PREVENTION OF FRACTURE IN MEN
1K02AG023582-01	KENT-BRAUN, JANE	Mechanisms of Skeletal Muscle Fatigue in Aging Adults
2R01AG012834-06A1	KIRWAN, JOHN	Age, Exercise, Diet: Effects on Insulin Resistance
1R03AG023890-01	KOCH, PATRICIA	Menstrual Health Disparities of Low SES African-America*
1R21AG024484-01	KRIKORIAN, ROBERT	Exercise and Cognitive Aging
1R01AG023139-01A1	KUEHL-KOVARIK, MARY	Functional changes in GnRH neurons with age
2P01AG004390-21A1	LIPSITZ, LEWIS	HRCA/Harvard Research Nursing Home
5R03AG023108-02	MAESTAS, NICOLE	The Economic Cost of Joint Retirement
5T32AG000262-07	MAGAZINER, JAY	Research Training in the Epidemiology of Aging
1F32AG025640-01	MAHAY, JENNA	Pathways Between Social Life and Health in Older Adults
1R01AG023522-01	MARMOT, MICHAEL	Health disparities and aging in societies in transition

1Z01AG000180-19	MCCRAE, ROBERT	Stress, Coping And Personality In Aging Men And Women
5R01AG019698-04	MOHAN, SUBBURAMAN	DETECTION OF THE SPONTANEOUS FRACTURE MOUSE MUTANT GENE
5R01AG013396-08	MONK, TIMOTHY	PHASE SHIFT TOLERANCE IN OLDER PEOPLE
5R01AG018436-05	MROCZEK, DANIEL	PERSONALITY AND WELL BEING TRAJECTORIES IN ADULTHOOD
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1R01AG022578-01A1	NEWTON, KATHERINE	HRT Decision Making in the Post-WHI Era
1R03AG023914-01	ORDOVAS, JOSE	Vitamin K: Genetics of Vascular Calcification
5R01AG011564-09	PAVALKO, ELIZA	WORK AND HEALTH AMONG MID-LIFE WOMEN
5R01AG014745-07	PETITTI, DIANA	Alzheimer's Disease and Estrogen Replacement
2R01AG017907-05A1	POLAN, MARY	Collagenolysis and Elastolysis in Urinary Incontinence
5P50AG005136-21	RASKIND, MURRAY	ALZHEIMERS DISEASE RESEARCH CENTER
1Z01AG000185-15	RESNICK, SUSAN	Early Markers Of Alzheimer Disease
1R13AG023743-01	RICH, MICHAEL	PRICE: Pivotal Research in Cardiology in the Elderly
1R03AG022624-01A1	ROESCH, DARREN	Ovarian Senescence and Adrenal Hormone Responses
7R01AG024058-02	ROGOWSKI, JEANNETTE	NEIGHBORHOODS AND THE HEALTH OF ELDERLY AMERICANS
1T32AG023475-01	ROSSETTI, LUCIANO	Training in Aging Research
5R01AG019291-04	SANDBERG, KATHRYN	HORMONAL REGULATION OF ANGIOTENSIN RECEPTORS
5R01AG015922-07	SANO, MARY	Alzheimer's Disease Prevention Trial with Estrogens
1K08AG024816-01	SCHERZER, CLEMENS	Genomic and Genetic Analysis of Parkinson's Disease
2R37AG013038-09	SEALS, DOUGLAS	Human Aging, Exercise & FMD: Translational Physiology
1Z01AG007170-07	SIMONSICK, ELEANOR	Treadmill Validation Of The Health ABC LDCW
5F31AG021329-02	SIMS, COLETTE	Health Access/Utilization Behavior of Older Black Women
5R01AG015478-07	SINGER, DANIEL	Epidemiology of Anticoagulation in Atrial Fibrillation
5P01AG022550-020004	SINGH, MEHARVAN	MECHANISM OF PROGESTERONE-INDUCED NEUROPROTECTION
5R01AG017104-05	SOWERS, MARYFRAN	FUNCTIONAL STATUS AND THE MENOPAUSAL TRANSITION
5R37AG021665-02	SOWERS, MARYFRAN	Estrogen, Metabolism, Menopause, and Health Outcomes
5R03AG022353-02	STEVENS, JUNE	Obesity in early and middle adulthood and retirement
5R01AG017919-05	SULLIVAN, EDITH	NORMAL AGING OF BRAIN STRUCTURE AND FUNCTION
5P01AG023028-02	SUSSER, EZRA	Early Determinants of Adult Health
1R03AG023286-01	SWINNEY, JEAN	Breast Cancer in African American Women 65 and Over
5R01AG020966-02	TANAKA, HIROFUMI	Resistance Training & Age-Related Arterial Stiffening

5P30AG010124-14	TROJANOWSKI, JOHN	Alzheimer's Disease Center Core
1R03AG022605-01A1	TROMMER, BARBARA	Estrogen, aging, and LTP in apoE replacement mice
5P01AG011412-09	VAN CAUTER, EVE	ALTERATIONS OF CIRCADIAN TIMING IN SLEEP AND AGING
5R37AG019695-03	VELDHUIS, JOHANNES	ACTIONS OF TESTOSTERONE ON THE AGING MALE GH AXIS
1R37AG023188-01A1	VLASSARA, HELEN	Effects of Glycoxidative Stress on Human Aging
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5R01AG017155-05	WHITE, LON	EPIDEMIOLOGY OF AGING AND DEMENTIA - AUTOPSY RESEARCH
5K08AG022788-02	WILLCOX, BRADLEY	Defining the Genetics of Exceptional Human Survival
5P01AG017164-05	WISE, PHYLLIS	FEMALE REPRODUCTIVE AGING: THE ROLE OF ESTROGEN
5T32AG000222-13	YANKNER, BRUCE	Training in the Molecular Biology of Neurodegeneration
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5U01AG021382-03	ZELINSKI-WOOTEN, MARY	Ovarian Aspects of Caloric Restriction
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1R01AG024154-01	HODIS, HOWARD	Biologic Response of Menopausal Women to 17B-Estradiol
5R01AG013204-08	VOYTKO, MARY LOU	Cognition and Estrogen in Menopause:A Monkey Model
5K01AG020683-03	MOREAU, KERRIE	HRT and Exercise Effects on Central Arterial Compliance
1R01AG022241-01A1	SEALS, DOUGLAS	HRT, SERMs and LEG BLOOD FLOW IN POSTMENOPAUSAL WOMEN
1P01AG024387-010001	HELFERICH, WILLIAM	GENISTEIN INDUCES ENDOCRINE-RESISTANCE IN BREAST TUMORS
2P01AG004875-210001	RIGGS, B. LAWRENCE%	PATHOPHYSIOLOGY OF OSTEOPOROSIS IN AGING WOMEN
5R01AG020082-03	VITIELLO, MICHAEL	PROGESTERONE AND SLEEP IN OLDER WOMEN
5R01AG014124-08	YOUNG, TERRY	Menopause and Midlife Aging Effects on Sleep Disorders
1R03AG023925-01	BIMONTE-NELSON, HEATHER	Progesterone, aging, and memory loss
5R01AG018339-05	VON MUHLEN, DENISE	DHEA REPLACEMENT IN HEALTHY OLDER MEN AND WOMEN
5R01AG018695-04	DUNN, JULIE	Estrogen, Vitamin E, and Cognitive Change in Women
1K23AG024254-01	HESS, RACHEL	Does Menopause Matter?
5R01AG017057-04	NEWTON, KATHERINE	ALTERNATIVE THERAPIES FOR MENOPAUSE: A RANDOMIZED TRIAL

1R01AG022578-01A1	NEWTON, KATHERINE	HRT Decision Making in the Post-WHI Era
5R01AG014745-07	PETITTI, DIANA	Alzheimer's Disease and Estrogen Replacement
5R01AG015922-07	SANO, MARY	Alzheimer's Disease Prevention Trial with Estrogens
5P60AG017231-050002	URBAN, RANDALL	Androgens and nutrition in older Americans
5K23AG019161-03	CAPPOLA, ANNE	Androgens, Myostatin, and Sarcopenia in Older Women
5R01AG017496-05	DOTY, RICHARD	POSTMENOPAUSAL ESTROGEN INFLUENCES ON OLFACTION
5R01AG017170-06	ELLIOT, SHARON	Estrogen Deficiency and REnal Disease in Aging Women
5R01AG019361-03	GOLD, ELLEN	Sleep during the peri-menopause in a multi-ethnic cohort
5R01AG019362-03	HALL, MARTICA	Sleep During the Perimenopause in a Multi-Ethnic Cohort
5R01AG018198-05	KOHRT, WENDY	MODULATION OF VISCERAL FAT BY ESTROGENS AFTER MENOPAUSE
5R01AG019363-03	KRAVITZ, HOWARD	Sleep During the Perimenopause in a Multi-Ethnic Cohort
2P01AG004875-210002	MELTON, L. JOSEPH III%	RISK FACTORS FOR HIP FRACTURES AMONG THE ELDERLY
5R01AG012161-10	SHAPSES, SUE	NUTRITIONAL REGULATION OF BONE TURNOVER
5R01AG014799-08	VELDHUIS, JOHANNES	THE AGING GH AXIS IN POSTMENOPAUSAL WOMEN
5R01AG018760-04	BEHAN, MARY	Age,Gender, Serotonin and Respiratory Control
2R44AG019082-02	EAKER, ELAINE	Testing An Interactive website for Hormone Replacement
5R01AG012611-10	JANOWSKY, JERI	The role of sex hormones on cognition
5R01AG018887-04	KENNY, ANNE	TESTOSTERONE FOR PREVENTION OF FRACTURE IN MEN
1R03AG022624-01A1	ROESCH, DARREN	Ovarian Senescence and Adrenal Hormone Responses
5R37AG019695-03	VELDHUIS, JOHANNES	ACTIONS OF TESTOSTERONE ON THE AGING MALE GH AXIS
5R01AG017196-06	ASTHANA, SANJAY	ALZHEIMER'S DISEASE: THERAPEUTIC POTENTIAL OF ESTROGEN
1R21AG023716-01	BINDER, ELLEN	Testosterone Therapy After Hip Fracture in Elderly Women
1K23AG024302-01	GLEASON, CAREY	Alzheimer's Disease: Potential Benefit of Isoflavones
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5R01AG020076-03	HOLLOSZY, JOHN	Is DHEA Replacement Therapy Beneficial?
5R01AG022008-02	RASGON, NATALIE	Estrogen Use in Protection from Cognitive Decline
5R01AG019310-04	RYAN, ALICE	Diet and Exercise: Race, Postmenopause and Metabolism
5R01AG015478-07	SINGER, DANIEL	Epidemiology of Anticoagulation in Atrial Fibrillation
1R03AG022605-01A1	TROMMER, BARBARA	Estrogen, aging, and LTP in apoE replacement mice
1F32AG023430-01A1	DUMAS, JULIE	Estrogen and Cognition In Postmenopausal Women
5R01AG020116-02	GOLDBERG, ANDREW	Race, Lipoprotein Lipase and Obesity after Menopause

5R01AG021543-02	HARLOW, SIOBAN	Staging Reproductive Aging in Five Cohort Studies
5R01AG015345-07	INSOGNA, KARL	Role of IL-6 in PTH-Induced Bone Resorption
5R01AG019327-04	KNOWLTON, ANNE	AGING, ESTROGEN, HSPS AND MYOCARDIAL ISCHEMIA
1R01AG023139-01A1	KUEHL-KOVARIK, MARY	Functional changes in GnRH neurons with age
2U01AG012495-11A1	MCCONNELL, DANIEL	Study of Women's Health Across the Nation-Endocrine Lab
2R01AG017907-05A1	POLAN, MARY	Collagenolysis and Elastolysis in Urinary Incontinence
1Z01AG000191-08	RESNICK, SUSAN	Neuroimaging Predictors Of Cognitive Change And Response
5R01AG019360-03	SOWERS, MARYFRAN	Sleep During the Perimenopause in a Multi-Ethnic Cohort
5K01AG019630-03	VAN PELT, RACHAEL	ESTROGEN, INSULIN AND REGIONAL LIPOLYSIS IN OLDER WOMEN
5-R01-AG012381-07	TAYLOR, THOMAS	Decision support for preventive hormone therapy
1-R43-AG017016-01	ZIMMERMAN, JANICE	Interactive media for women considering hormone therapy

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National Institute on Alcohol Abuse and Alcoholism

(NIAAA)

Grant No.	*Title*	*Principle Investigator*	*Site*	*Abstract*
	Tivis, Laura J.	Alcohol, ERT and Cognition in Menopausal Women	University of Oklahoma Hlth Sciences Ctr.	Applicants Abstract: A large proportion of postmenopausal women are at least moderate consumers of alcohol and exogenous estrogen (or lack of) on their cognitive functioning and psychological characteristics. Our first two aims are to determine whether drinking or use of estrogen replacement therapy (ERT) independently affect cognition in postmenopausal women. The third aim is to determine whether or not there are interactive effects of alcohol and ERT and if so, to determine the nature of their influence on cognitive processes. We also propose to investigate whether or not use of progestin replacement therapy (PRT) affects cognitive functioning. Four groups of postmenopausal women will be recruited; teetotalers, light moderate, and moderate heavy drinkers. Within each of the alcohol-drinking groups, 54 will ERT, 54 will be non-users. To accomplish aim 6 the teetotalers group will contain 54 non-users and 108 ERT users (54 ERT/no PRT and 54 ERT/PRT users). Alcohol use patterns are assessed. A battery of tests that measures specific neurocognitive processes will be used. Dependent variables will include accuracy, response times, and error type. Blood levels of estradiol and estrone will be measured and also used as dependent variables. Questionnaires pertaining to psychosocial characteristics will be administered. Psychosocial measures include demographic characteristics, employment history, satisfaction with family and work environments, health history, and recent life-change events. Psychosocial subscales scores will be used as dependent variables. Long-term benefits will include identification of risks and or benefits to cognition and psychosocial status associated with moderate drinking and use of ERT. These results can add to existing knowledge and provide an increased understanding of issues surrounding women's health care.
AA004610	Wilsnack, Sharon C.	Problem Drinking in Women – A 20-Year National Study	University of North Dakota	This application proposes a national survey of 1,550 women in 2001 to increase knowledge about longitudinal patterns of women's drinking. The survey will include 700 women interviewed in 1981 and 1991, 350 women first interviewed in 1991, and a new same of 500 women age 21-30 in 2001. (Subsamples of women were also interviewed in 1986 and 1996). Combining the 2001 survey with the preceding surveys will produce 20-yearcross-sectional data for all age groups, 20-year multiwave longitudinal data from women over age 40 in 2001, and 10-year longitudinal data from women age 31-40 in 2001. Specific aims of the proposed research are to evaluate (1) 20-year trends and age, period and cohort effects in women's drinking behavior; (2) predictors of 5-, 10- and 20-year age specific changes in women's drinking behavior; (3) effects on and from women's drinking trajectories across the adult life span; (4) correlates and predictors of heavier drinking among older women and among women of childbearing age; (5) effects of question formats and interview modes on women's drinking self-reports; (6) links of women's drinking patterns with disordered eating behavior and with use of prescribed psychoactive drugs; and (7) cross-national variations in women's drinking behavior and its antecedents and consequences, using data from an international collaborative project coordinated by our research group. In the 2001 survey, professional female interviewers will conduct 75- minute face-to-face interviews using many questions from previous surveys about drinking patterns, drinking-related problems, changes in work and family roles, depressive symptoms, sexual and reproductive experience and relationships with significant others. New questions will include a measure of trait impulsivity and additional questions about binge eating, estrogen replacement therapy, antidepressant use, and health problems of older age. Data analysis will include cross-tabular correlational and regression analyses; analysis of variance; cluster analysis (of drinking partnerships and drinking trajectories); structural equation modeling (for longitudinal prediction of 2001 drinking patterns); and generalized estimating equation, random regression models, latent transition analysis, and survival analysis (for comparing trends and trajectories and for predicting trajectories). The 2001 survey, combined with data from the 1981, 1986, 1991, and 1996 surveys, will yield the largest, longest-term and most detailed set of longitudinal and life-historical data yet available about U.S. women's drinking and its antecedents and consequences. Together with findings from the international collaborative gender and alcohol project, issues addressed by the proposed analyses of these data should provide a strong foundation for efforts to improve the prevention and treatment of women's problem drinking in the 21st century.
AA000219	Berman, Marlene O.	Affective and Conative changes in Alcoholism	Boston University	This is an application for an ADAMHA Senior Scientist Award (SSA). The SSA would permit the PI (a) to devote all of her research efforts to alcoholism; (b) to expand her research and mentoring activities concerned with gender issues in alcoholism; and (c) to gain valuable experience with structural and functional neuroimaging techniques. In conjunction with 2R01 AA 07112-09, investigations are planned to examine changes in affect (emotion) and conation (intention) in abstinent alcoholics. Secondary aims of the research are to expand studies of age-related changes and gender differences in emotional and intentional functions. The importance of the research is fourfold: (1) Putative sites of alcohol-related brain damage involve separate frontal systems which are tied to different perceptual/cognitive aspects of emotional and intentional behaviors; (2) gender differences in alcohol-related neurobehavioral functions are ripe for experimental exploration; (3) the literature on whether emotional changes have reciprocal effects on perception and cognition in alcoholism is equivocal and controversial; and (4) even though affective and conative abnormalities have been clinically apparent in alcoholic groups, neuropsychological studies have focused primarily on cognitive changes unrelated to emotion and intention. In the proposed experiments we will enlist the participation of right-handed male and female research subjects ranging in age from 20 to 75 years. The experimental groups will include abstinent alcoholics with and without Korsakoff's syndrome. Patterns and levels of performances by the alcoholics will be compared to those of age-matched nonalcoholics subjects, in order to evaluate the ways in which behavioral consequences of aging and alcoholism are parallel, divergent or interactive. Additionally, patients with right-frontal or bilateral frontal lobe damage from cerebrovascular accidents will provide the necessary control comparisons for neurobehavioral changes linked directly to focal brain damage. These groups were chosen specifically to clarify frontal system contributions to deficits of Korsakoff and non-Korsakoff alcoholics. We also will be able to evaluate hypotheses about greater right-than left-hemisphere functional decline in the alcoholic and aging groups, and in women compared to men. It is expected that results of the proposed studies will show clear evidence of frontal-mediated affective and conative changes in alcoholics (most notably in the Korsakoff patients), but that these changes will not be conspicuous in aging populations uncomplicated by alcoholism. By the contrast, certain aspects of perceptual functioning will be compromised by aging whether or not a history of alcohol abuse already exists. Finally, women will display different performance patterns than men.

Grant No.	*Title*	*Principle Investigator*	*Site*	*Abstract*
AA011954	Helzer, John E.	Enhancing Brief Intervention of Primary Care Physicians	University of Vermont & St. Agric College	Interactive Voice Response (IVR) is a computer-based telephone technique that allows subjects to respond to a recorded voice asking scripted questions. The caller inputs brief numeric answers using the telephone touch pad. In a series of studies, we have been using the IVR as a reporting device to examine the evolution of alcohol consumption over time and its relation to alcohol problems. In this study we propose to test IVR in a primary care practice as treatment tool to enhance physicians' brief alcohol interventions with heavy and problem drinkers. Method: after brief alcohol intervention by their physician in participating primary care clinics, consenting patients meeting our selection criteria will be randomized to one of four study groups. The first three of these are: 1) Brief intervention only: II) Brief intervention plus daily calls by the subject to the IVR: III) Brief intervention plus daily IVR calls with periodic feedback of IVR consumption data to the patient via the physician. Group IV will receive the same treatment as group III, but subjects in Group IV will receive a financial incentive to help ensure a high IVR call compliance rate. Goals: We will assess: 1) The feasibility of using IVR as an intervention in primary care patients including call compliance rates and the validity of the consumption reports, and 2) Whether an IVR with or without patient feedback enhances the effects of a brief alcohol intervention by a physician. Our long-term objective is to develop interventions specifically designed to capitalize on the unique advantages of an IVR system. The public health implications of effective, low cost interventions for heavy and problem drinking that can be accessed remotely and are applicable in primary care and HMO settings and considerable
AA014441	Abdel-Rahman, Abdel A	Mechanisms of Alcohol-Estrogen Hemodynamic Interaction	East Carolina University	Alcohol elicits unique cardiovascular responses in the female population that are not only different from those seen in males but are also significantly influenced by the ovarian hormones, particularly estrogen. The objective of this proposal is to elucidate the molecular mechanisms implicated in the estrogen-dependent hemodynamic responses elicited by ethanol in female rats. Given the remarkable resemblance of the estrogen-dependent hemodynamic responses elicited by ethanol to the manifestations associated with mild endotoxicemia, we hypothesize that the NOS-NO signaling pathway plays a pivotal role in these responses. To test this hypothesis, we propose to conduct a series of integrative, signal transduction and gene expression studies under three aims. Aim 1 tests the hypothesis that activation of the vascular and/or cardiac nitric oxide synthases (NOS) mediates the estrogen-dependent hypotension and myocardial depression caused by acute alcohol in female rats. Since increased production of NO in the nucleus tractus solitarius (NTS) elicits hypotension, aim 2 studies will test the hypothesis that overproduction of NOS-derived NO in the NTS caused by additive or synergistic ethanol-estrogen interaction is implicated in the hypotensive and baroreflex depressant effects of acute ethanol in female rats. Aim 3 studies will identify the cellular mechanisms implicated in the chronic estrogen-dependent hypotensive and baroreflex depressant effects of ethanol in a model of surgical menopause. The proposal adopts a well-designed experimental approach that incorporates an established animal model, appropriate controls, and pharmacological interventions to: (i) establish a causal relationship between the up-regulation of NOS-derived NO in peripheral cells (myocyte and vascular smooth muscle) and neurons (NTS) and the estrogen-dependent cardiovascular effects of ethanol, and (ii) identify the molecular mechanisms implicated in the actions of ethanol, estrogen and their combination on NOS-NO signaling. The proposed research, whose primary focus is to probe the molecular mechanisms of estrogen-dependent hemodynamic effects of ethanol, addresses in a timely manner a significant biomedical problem and is expected to yield clinically relevant information.
AA005965	Pfefferbaum, Adolf	CNS Defects-Interaction of Age and Alcoholism	SRI International	DESCRIPTION: We propose to continue using magnetic imaging (MRI), neuropsychological (NP) and event-related potential (ERP) testing to extend and refine our findings of CNS deficits associated with chronic alcoholism and aging. Our MRI studies of alcoholic man reveal volume loss in cortical gray and matter, corpus callosum, hippocampus, and mammillary bodies and enlargement of cortical sulci and lateral and third ventricles. Older alcoholic men have gray matter volume deficits particularly striking in the prefrontal cortex. Electrophysiologically, the latency of P300, a physiological index of cognitive speed, is prolonged in alcoholic men with an exaggerated prolongation in older alcoholics; further P300 latency and indices of tissue loss are significantly associated in alcoholics. Neuropsychologically, alcoholic men show deficits in executive abilities, short-term memory, fluency and visospatial abilities and especially severe deficits in balance. Our longitudinal studies demonstrate recovery of gray matter volume with abstinence and further reduction of white matter volume with continued drinking. For the competitive renewal, we propose the following studies: Study 1: fMRI experiments of localized brain activation during performance of auditory and visual working memory tasks. This study is designed to determine whether alcoholics show a pattern of cortical activation during working memory that is different from that observed in controls, and whether underlying structural deficits influence the pattern of fMRI activation. Study 2: Visual ERP and NP experiments of the interhemispheric transfer time designed to assess the functional significance of corpus colossal thinning. Study 3: Continuation of our ongoing longitudinal study of alcoholic and control women. This study is designed to identify cross sectional patterns of sparing and loss, their interaction with age and their comparability to findings in alcoholic men. Cross-sectional findings will be examined longitudinally to determine their interaction with alcohol consumption and the normal course of aging and to assess the extent to which deficits normalize with sobriety or are exacerbated with continued drinking. Study 4: A new longitudinal study in a new sample of older alcoholic men and women and their controls in order to extend with refined anatomical and new functional measures earlier findings.
AA014039	Nixon, Sara	Moderate Alcohol in Older Adults: A Preliminary Study	University Kentucky Lexington	Despite the recognition that the cohort of older adults continues to increase, that older adults remain socially and professionally engaged for longer periods of time and that alcohol may adversely interact with common medications and various functions, systematic research on moderate alcohol use in older populations is remarkably limited. It is restricted by narrow test batteries, the inclusion of largely male samples and/or the failure to recruit representative samples. This revised pilot study was designed to address some of these limitations. Specifically, it would provide critical preliminary data regarding the effects of the acute administration of moderate alcohol and the effects of continued moderate drinking on neurocognitive, neurophysiological, and psychomotor performance as well as psychosocial functioning and adaptation. To complete this initial work, 148 older moderate drinkers between the ages of 56 and 70 will be evaluated. 132/148 will be tested under a double-blind placebo-controlled design. The remaining 16 (8 male/8 female) will comprise a comparison group to be tested under control conditions where alcohol is neither expected nor administered, Because older women are a particularly understudied group, every attempt will be made to recruit equal numbers of male and female drinkers. Data collected from this study will provide critical information regarding the effects of acute, moderate doses of alcohol on older drinkers in a variety of domains and will also provide comparison data with younger substance abusing and community control subjects evaluated in our on-going work. This project, by ensuring appropriate protocol development, training, pilot work and initial data collection, would provide the necessary foundation for the further development of an aging focus in our on-going research program.

Grant No.	*Title*	*Principle Investigator*	*Site*	*Abstract*
AA000115	Hibbeln, Joseph R.	Essential Fatty Acids In Psychiatric Disorders	National Institute On Alcohol Abuse And Alcoholism LMBB	This project examines whether inadequate dietary intakes of omega-3 essential fatty acids increases the risk for pathological behaviors associated with alcoholism, specifically depression, aggression and suicide. Randomized placebo controlled clinical interventional trials continue to be conducted in adult populations among aggressive alcoholics, **women** with depression during pregnancy and suicide attempters. These studies have been stimulated by the discovery of large differences in the prevalence rates of several psychiatric disorders when comparing populations with high or low measure of seafood consumption and from examinations of omega-3 fatty acid tissue concentrations in epidemiological studies. Nutritional inadequacies during early development may leave residual neuropsychiatric deficits which contribute to an increased predisposition toward psychiatric disorders in adulthood. Developmental outcome studies are discussed below. In our ongoing clinical trial of aggressive alcoholics, the key questions are to assess if treatment with 2.8 g/d of omega-3 fatty acids will reduce 1) aggressive behaviors, 2) improve neurochemical measures of serotonergic function 3) improve cardiovascular measures thought to be associated with depressive and violent behaviors. This protocol is active and has enrolled 19 subjects with a 100% tracking of data. Preliminary results are not available until completion until the blind is broken. Completion of the study is estimated for Fall 2005. In collaboration with Garth Bissett, Ph.D. we determined that low plasma DHA levels predict elevated levels of corticotrophin releasing **hormone** in the CSF of perpetrators of domestic violence. This finding, now in press, may lead to down regulation of the HPA axis through dietary changes. This proposition is currently being tested in a placebo-controlled, intervention trial of aggressive alcoholics. In collaboration with Laure-Budens Branchey, M.D. we published that a low plasma levels of DHA and AA predicted relapse among cocaine and alcohol dependent subjects over the course of two years. We are collaborating with Dr. Branchey to determine if supplementation with omega-3 fatty acids will actually reduce relapse in a randomized controlled trial. Mothers can become depleted of omega-3 essential fatty acids during pregnancy when their dietary intake is inadequate. Dietary deficiencies may increase the risk of depressive symptoms for the mothers. 1) Preliminary data is available from an open trial of omega-3 fatty acids among **women** with depression during pregnancy currently being conducted in collaboration with Marlene Freeman, MD at the University of Arizona. Depressive symptoms were reduced an average of 43.5 % during 8 weeks of treatment. These findings are significant as they offer a treatment for depression during pregnancy that is not only non-toxic, but has additional health benefits to pregnant **women** and their babies. These findings are being followed up with a randomized, controlled trial. The results of these interventional trials were predicted from data from an epidemiological study of the dietary intake of omega-3 fatty acids during pregnancy among nearly 14,000 **women** enrolled in the Avon Longitudinal Study of Parents and Children (ALSPAC). In clear dose-response relationships, deficient intakes were associated with nearly a doubling of the risk of depressive symptoms (EPDS >12) at 32 weeks gestation ($p<1.4 \times 10^{-17}$) and 18 weeks gestation and at both 8 weeks and 8 months postpartum. Findings were robust after rigorous examination of potential confounding factors. Deficient intake of omega-3 essential fatty acids during early development may also have adverse residual effects on the behaviors of children. 1) In collaboration with the ALSPAC study, we found that deficient intake of omega-3 fatty acids during pregnancy were related to a doubling of the risk of adverse behaviiioral disorders among children at both 3.5 and 7 years of age. A dose response relationship predicted such parameters as increased risk of conduct disorders: fighting, lying, stealing, disobedience, which are well recognized risk factors for future sociopathic and criminal behaviors. We have collaborated with Marc Schuckit, M.D and Jean Golding, Ph.D. in designing a study to prospectively capture initial drinking behavior of these children as they enter adolescence. These data can be evaluated to determine if inadequate intake during pregnancy or early childhood is a risk factor for future substance abuse. If this is identified as a risk factor, prevention studies can be planned. A significant finding was that compliance with the FDA and EPA methyl mercury advisory for **women** to limit seafood consumption during pregnancy inadvertently creates harm in the specific developmental domains in which it was intended to provide protection. The ALSAPC study was examined by either compliance or exceeding intake described by the advisory. These finding are currently being prepared for publication. In a prior cross-national analysis we found higher rates of homicide mortality were correlated to lower rates of seafood consumption. In order to further refine this finding we utilized the observation that the omega-6 fatty acids from seed oils compete for space in the tissues with omega-3 fatty acids which are rich in seafood. We found that from 1950 to 2000, the increasing rates of homicide mortality were closely correlated with increasing availability omega-6 fatty acids in the food supply, in the USA, the United Kingdom, Australia and Canada. This association is also consistent with observational and interventional data for violence and hostility published by other investigators. 2) In collaboration with Dr. Carlos Iribarren, we examined the dietary intake of omega-3 fatty acids and behavioral correlates among the 4,000 subjects in the CARDIA trial, lower intake of DHA and other omega-3 fatty acids predicted a doubling of the risk of reporting clinically significant measures of hostility. 3) In an interventional trial conducted in collaboration with Dr. Muldoon at the University of Pittsburgh, subjects with hypercholesterolemia were given either Simvistatin, (a cholesterol lowering drug) or a placebo for 8 weeks. We quantified changes in mood, cognition and plasma concentrations of essential fatty acids. Treatment with Simvistatin lowered total fatty acid concentrations, but spared DHA and AA. The relationship between the sparing of these essential fatty acids and improvements or decrements in mood and cognition are still under examination.
AA014211	Colrain,, Ian	Alcoholism, Sleep and the Brain	SRI International	Acute and chronic alcohol consumption causes sleep disturbances, which may never resolve and may be a key factor in alcoholism relapse. Alcohol-related sleep deficits also become more pronounced with advancing age. The most consistently reported finding of altered sleep in alcoholics is a reduction in spontaneously occurring slow wave sleep (SWS), defined by the presence of delta EEG activity. Further, alcoholics with reduced baseline SWS have an increased likelihood of relapse. External stimulation during sleep can elicit K-complexes, which when averaged produce a large N550 component thought to have the same generator as SWS delta activity. Given the potential value of sleep markers in predicting relapse, it would be advantageous to employ a probe of the sleeping nervous system that can be under experimenter control rather than one that relies on the traditional observation of spontaneous sleep physiological indices. We have demonstrated that sleep-evoked N550 component amplitudes are smaller and K-complexes are produced on a smaller number of trials in elderly than young controls. Our preliminary study indicates that alcoholics have even smaller N550 than would be expected for their age. A candidate generator of the K-complex and N550 is frontal cortical gray matter, which is especially reduced in older alcoholics. Sex differences in brain structure and electrophysiological indices of sleep also occur in alcoholism and **aging**, and objective study of them may further contribute to our understanding of relevant mechanisms of alcoholism-related sleep disturbance. We propose to test the following hypotheses: Hypothesis 1: Recently detoxified, chronic alcoholics will have smaller N550 amplitudes, lower evoked K-complex proportions, lower SWS levels and delta EEG power compared to sex- and age-matched controls. Hypothesis 2: Low evoked K-complex production rates, small N550 amplitude, low SWS levels and delta EEG power will be associated with small prefrontal gray matter volume. Hypothesis 3: Alcoholic men will have greater sleep abnormalities than alcoholic **women**. Hypothesis 4: Small amplitude, production rate and power of sleep electrophysiological variables in recently detoxified alcoholics will predict early relapse.

National Institute of Allergy and Infectious Diseases

(NIAID)

National Institute of Allergy and Infectious Diseases

Menopause Related Research

The NIAID Division of Allergy, Immunology, and Transplantation has an active interest in the sex based differences in the immune response, including the effects of sex hormones on immunologic function. Autoimmune diseases, which result from a disordered attack of the immune system on the body's own tissues, affect an estimated 5 to 8 percent of the U.S. population and disproportionately afflict women. Ongoing relevant studies include:

1. **Sex hormone regulation of innate immunity, P01-AI-051877, PI: Charles Wira, Dartmouth Medical School**

   The overall objective of this Program Project is to define the role of sex hormones (androgens, estrogens and progestins) in regulating the innate immune system as it functions systemically and at mucosal surfaces. Mechanisms whereby sex hormones influence phenotype, innate function, and communication between the innate and adaptive immune systems will be defined. Peripheral blood cells from men and women, cell lines, and immune cells and tissues from the female reproductive tract will be utilized to define the role of sex hormone and pathogenic challenge at the cellular and molecular level. The hypothesis is that innate immunity (epithelial cells, neutrophils, macrophages and NK cells) is under male and female sex hormone control and that, in addition to conferring protection, each of these cells is capable of initiating an adaptive immune response.

2. **Protein targets of ovarian and oocyte autoantibodies, R01-AI-055060, PI: Judith Luborsky, Rush Medical College**

   Ovarian autoimmunity may affect 1-2 million women in the US. In order to identify women with ovarian autoimmunity, prototype immunoassays were developed to detect ovary specific autoantibodies. The results were used to develop phenotypic information on the association of ovarian autoimmunity with premature menopause (premature ovarian failure) and unexplained infertility.

   Further human research and clinical use depends on identification of the relevant protein antigens. The objective of the proposed study is to identify major autoantigens relevant to the phenotypes associated with ovarian autoimmunity. Previous studies showed that ovarian antibodies are associated with a low likelihood of pregnancy after infertility treatment. The proposed study is expected to improve the precision with which ovarian autoimmunity is detected. This will permit studies of disease

   pathogenesis, health risks associated with ovarian autoimmunity, genetic factors associated with disease susceptibility, and improve clinical diagnosis. It will also

contribute to a better understanding of an autoimmune disease that affects women's health.

3. **Molecular consequences of estrogen-induced interferon, R01 AI051880, PI: Ansar Ahmed, Virginia Polytechnic Institute and State University**

Sex hormones, such as estrogens, are believed to play a major role in gender-based differential immune competence and autoimmunity. One mechanism by which estrogens may influence the immune system is by regulating cytokine levels. This grant is aimed at mechanistically studying how estrogen alters the production of interferon and the molecular consequences of increased interferon Estrogen-induced interferon is significant, since interferon is a "master" cytokine with physiological effects on nearly all cells of the immune system. This project will examine the molecular basis for production and action of estrogen-induced interferon.

4. **Sex-based differences in the immune response, R01 AI 051767, PI: Betty Diamond, Yeshiva University**

It has long been hypothesized that sex hormones play a role in immune regulation and specifically in systemic lupus erythematosus. Estrogens can alter the threshold for negative selection of naive autoreactive B cells and may thus influence the development of autoimmune diseases. This project will examine how estrogen leads to an increase specifically in cells of the marginal zone B cell subset. In addition, experiments will be conducted to investigate the differences in B cell responsiveness to estrogen in different mouse strains to understand what underlies an estrogen-mediated breakdown in humoral self- tolerance.

5. **Sex-based differences in regulatory T cell responses, R21 AI 051870, PI: Michele Kosiewicz, University of Louisville**

Many autoimmune diseases are much more prevalent in women compared to men, including multiple sclerosis, arthritis and systemic lupus erythematosus. Although the reason for this difference is not currently known, the sex hormones are likely to play a significant role. A recently described population of naturally occurring regulatory T cells, CD4+CD25+, is responsible for controlling autoimmune disease in mice. Elimination of this population in mice results in severe multi-organ autoimmune diseases. This project will test the hypothesis that sex steroids mediate the gender differences in CD4+ CD25+ regulatory T cells, and through this mechanism may influence the differential expression of autoimmune disease in females versus males. The results of these studies will provide important information that can lead to the development of novel therapies for the prevention and treatment of autoimmune disease.

6. **Sex hormone regulation of the mucosal immune system, 5 R37 AI013541-23, PI: Charles Wira, Dartmouth**

The broad objectives of the research proposed in this application are to understand at the cellular and molecular levels, the physiological actions of sex hormones on the mucosal immune system. These actions account for changes in humoral and cellular immunity and

have clinical applications in the treatment of venereal diseases, autoimmune diseases, malignancy, infertility and fertility control. Studies will be undertaken to: (1) examine the regulation by sex hormones and antigens of immune cells in the female reproductive tract; (2) elucidate the role of selected cytokines in the response of the genital tract to antigens and identify the way in which they interact with sex hormones to influence mucosal immunity; (3) identify the mechanism(s) responsible for estradiol-regulated movement of IgA and IgG; and (4) study the role of sex hormones antigens and cytokines in regulating secretory component (SC) and IgA gene expression.

Current Publications

1. Shen L, Fahey JV, Hussey SB, Asin SN, Wira CR, Fanger MW. Synergy between IL-8 and GM-CSF in reproductive tract epithelial cell secretions promotes enhanced neutrophil chemotaxis. Cell Immunol. 2004 Jul; 230(1):23-32.
2. Schaefer TM, Desouza K, Fahey JV, Beagley KW, Wira CR. Toll-like receptor (TLR) expression and TLR-mediated cytokine/chemokine production by human uterine epithelial cells. Immunology. 2004 Jul; 112(3):428-36.
3. Eriksson M, Meadows SK, Wira CR, Sentman CL. Unique phenotype of human uterine NK cells and their regulation by endogenous TGF-beta.
J Leukoc Biol. 2004 Sep; 76(3):667-75. Epub 2004 Jun 03
4. Crane-Godreau MA, Wira CR.Effect of Escherichia coli and Lactobacillus rhamnosus on macrophage inflammatory protein 3 alpha, tumor necrosis factor alpha, and transforming growth factor beta release by polarized rat uterine epithelial cells in culture. Infect Immun. 2004 Apr; 72(4):1866-73.
5. Peeva E, Venkatesh J, Michael D, Diamond B. Prolactin as a modulator of B cell function: implications for SLE. Biomed Pharmacother. 2004 Jun; 58(5):310-9.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

(NIAMS)

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Menopause Research FY 2003-2004

Overview

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases, the training of basic and clinical scientists to carry out this research, and the dissemination of information on research progress in these diseases. Many of the diseases in our research portfolio disproportionately affect women, particularly menopause-related conditions such as osteoporosis. The NIAMS is committed to uncovering the scientific bases of these disparities and to devising effective strategies to treat or prevent them through a broad portfolio of menopause- and hormone-related research.

Osteoporosis is a skeletal disorder marked by reduced bone strength that predisposes a person to an increased risk of fractures. Osteoporosis poses a major public health challenge for both women and men. Women, in particular, have and increased risk of developing osteoporosis because of accelerated bone loss at menopause. NIAMS supports a broad portfolio of grants focused on our understanding of the relationship between menopause and osteoporosis. Specific examples include research examining the impact of exercise on bone mineral density (BMD). Recent studies have shown that aerobic, weight-bearing and resistance exercise improves BMD in postmenopausal women whether or not they use hormone therapy. Other NIAMS-supported researchers are exploring the cellular and molecular basis of parathyroid hormone (PTH) on bone. PTH is a medication used to treat osteoporosis and has been shown to stimulate new bone formation. NIAMS-supported researchers are also exploring new areas of research including the effects of soy on bone in non-osteoporotic early postmenopausal women. Additional research is focusing on the signaling pathways involved in bone formation and bone loss. An improved understanding of these pathways could furnish new principles for the development of measures to improve bone quality and prevent menopause-associated osteoporosis.

FY 2003-2004 Menopause Research Advances

Exercise Builds Bone Mass in Postmenopausal Women Whether or Not They Use Hormone Therapy

NIAMS-supported investigators conducted a randomized clinical trial in 320 postmenopausal women between the ages of 45 and 65 to test the effect of a specific exercise regimen on bone mineral density. The women who were randomized to the exercise regimen – a combination of weight-bearing and resistance exercises – showed significant improvement (1 to 2 percent) in BMD after one year at the hip and spine, two important sites of fractures that may result from the osteoporosis. Notably, this benefit was found in both women taking postmenopausal hormone therapy and those who did not, although the women taking hormones had a somewhat greater response to exercise.

The study shows that specific strength training and resistance exercises can retard and even reverse bone loss in healthy postmenopausal women, and that estrogen replacement is not necessary to gain the benefit of the exercise. All women received calcium supplements, and adequate calcium may be a factor in optimizing the effect of exercise on bone in postmenopausal women. These findings may provide reassurance for women who no longer take hormone replacement therapy because of the recent Women's Health Initiative findings.

Inhibiting Enzyme Increases Bone Density

NIAMS-supported researchers have used a combination of mouse breeding and genetic technology to identify a gene that strongly influences peak bone mass in mice. The gene, which is present in humans as well as mice, was not previously known to be involved in bone biology, and hence represents a promising new target for development of drugs that could prevent or reverse the bone loss that leads to osteoporosis. Peak bone mass, acquired early in life, is thought to be an important factor in the risk for osteoporosis in humans.
Researchers studied the offspring of a mating between mouse strains with markedly different peak bone mass, and identified a particular region of one chromosome which influences peak bone mass. Subsequently, their studies of the genes located within this region showed that the Alox15 gene, which produces an enzyme called 12/15-lipoxygenase (12/15-LO), was much more active in the low-bone mass strain than in the high-bone mass strain. Follow-up experiments confirmed the effects of 12/15-LO on bone mass in mice.

In a further phase of the study, the researchers investigated the effect of pharmacological inhibitors of the 12/15-LO enzyme. These drugs had already been developed to inhibit 12/15-LO in other conditions, such as atherosclerosis (clogged arteries), cancer, and asthma, in which this enzyme is also thought to play a role. The use of these drugs resulted in an increase in BMD throughout the body in mice that were estrogen-deficient after removal of the ovaries. Reduction in estrogen production with menopause is the major cause of loss of BMD during later life. While further animal and human investigation into the role of 12/15-LO in the development of osteoporosis is needed, the results of this study suggest that inhibition of 12/15-LO may play a role in osteoporosis treatment and prevention.

NIAMS-Supported Menopause Grants FY 2003-2004

Grant Number	PI Name	Institution	Project Title
AR042540	BUYON, JILL P.	HOSPITAL FOR JOINT DISEASES ORTHO INST	SAFETY OF ESTROGEN IN LUPUS ERYTHEMATOSUS-NAT'L ASSESS'
AR049701	MAJUMDAR, SHARMILA	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	VERTEBRAL FRACTURE: TRABECULAR BONE STRUCTURE ASSESSMENT
AR046859	PREVRHAL, SVEN	UNIVERSITY OF CALIFORNIA SAN FRANCISCO	MEASUREMENT OF THICKNESS/DENSITY OF THE PROXIMAL FEMUR
AR050618	SNYDER PETER J	UNIVERSITY OF PENNSYLVANIA	WILL TESTOSTERONE /GROWTH HORMONE IMPROVE BONE STRUCTURE

AR048205	VOKES TAMARA	UNIVERSITY OF CHICAGO	CLINICAL UTILITY OF TEXTURE ANALYSIS IN OSTEOPOROSIS
AR044855	KRONENBERG, HENRY M	MASSACHUSETTS GENERAL HOSPITAL	SPECIALIZED CENTER FOR RESEARCH IN OSTEOPOROSIS
AR041325	BOSKEY, ADELE	HOSPITAL FOR SPECIAL SURGERY	FT-IR MICROSCOPY OF MINERAL STRUCTURE IN OSTEOPOROSIS
AR042906	BROOKS, GEORGE	UNIVERSITY OF CALIFORNIA BERKELEY	EXERCISE SUBSTRATE UTILIZATION: THE CROSSOVER CONCEPT
AR050662	CHANG, WENHAN	NORTHERN CALIFORNIA INSTITUTE RES & EDUC	RESOLUTION OF STAGE-SPECIFIC GROWTH PLATE CHONDROCYTES
AR049633	GOLTRY, KRISTIN L	AASTROM BIOSCIENCES, INC.	CLINICAL-SCALE PRODUCTION OF OSTEOPROGENITOR CELLS
AR050352	KINDLE, LIBBY A	WASHINGTON UNIVERSITY	RECRUITMENT OF OSTEOCLASTS FROM BONE MICROVASCULATURE
AR050001	LI, YEFU	HARVARD UNIVERSITY (MEDICAL SCHOOL)	GENETIC REGULATION OF SKELETOGENESIS
AR049341	LICHTLER ALEXANDER	UNIVERSITY OF CONNECTICUT SCH OF MED/DNT	DLX GENE REGULATION OF OSTEOBLAST DIFFERENTIATION
AR046032	NAFTOLIN, FREDERICK	YALE UNIVERSITY	AROMATASE INHIBITOR METHYL TESTOSTERONE AND TESTOSTERONE INDUCED BONE SPARING
AR050201	PENG, HAIRONG	CHILDREN'S HOSP PITTSBURGH/UPMC HLTH SYS	IMPROVING BONE HEALING BY MYOFIBER DEDIFFERENTIATION

AR048833	TURNER, RUSSELL T	MAYO CLINIC COLL OF MEDICINE, ROCHESTER	ETIOLOGY AND TREATMENT OF PARATHYROID BONE DISEASE
AR092237	RECKER, ROBERT M.	CREIGHTON UNIVERSITY	HORMONE REPLACEMENT THERAPY WITH ALENDRONATE IN POST MEN
AR046922	ALEKEL, LEE D	IOWA STATE UNIVERSITY OF SCIENCE & TECH.	BONE RESPONSE TO SOY ISOFLAVONES IN WOMEN
AR044655	BECK, THOMAS J.	JOHNS HOPKINS UNIVERSITY	STRUCTURAL ANALYSIS OF DEXA SCANS: OSTEOPOROSIS STUDIES
AR051702	BHATTACHARYA AMIT	UNIVERSITY OF CINCINNATI	A NOVEL POST-MENOPAUSAL OSTEOPOROSIS SCREENING TOOL
AR051483	BROWN SUE A	UNIVERSITY OF NORTH CAROLINA CHAPEL HILL	BONE ACCRUAL AND HORMONES IN RESPONSE TO LACTATION
AR50496	DENG HONG-WEN W	CREIGHTON UNIVERSITY	ROBUST AND POWERFUL TEST OF CANDIDATE GENES TO BONE MASS
AR48826	FRAENKEL LIANA	YALE UNIVERSITY	ELICITING PATIENT TREATMENT PREFERENCES FOR OSTEOPOROSIS
AR035584	HOCHBERG, MARC C	UNIVERSITY OF MARYLAND BALT PROF SCHOOL	OSTEOPOROTIC FRACTURES
AR027065	KHOSLA, SUNDEEP	MAYO CLINIC ROCHESTER	EPIDEMIOLOGY OF AGE RELATED BONE LOSS AND FRACTURES
AR041398	KIEL, DOUGLAS P.	HEBREW REHABILITATION CENTER FOR AGED	RISK FACTORS FOR AGED RELATED BONE LOSS

AR048841	LANE, NANCY	UNIVERSITY OF CALIFORNIA SAN FRANCISCO	MIDCAREER INVESTIGATOR AWARD PATIENT-ORIENTED RESEARCH
AR50298	SIBONGA JEAN D	MBC RESEARCH, INC.	PREVENTION OF OSTEOPOROSIS WITH NOVEL BISPHOSPHONATES
AR051564	WREN TISHYA AL	CHILDREN'S HOSPITAL LOS ANGELES	MECHANICAL INTERVENTION IN CHILDREN WITH CEREBRAL PALSY
AR051124	ZMUDA JOSEPH M	UNIVERSITY OF PITTSBURGH AT PITTSBURGH	BONE STRENGTH PHENOTYPES IN MEN: GENES AND ENVIRONMENT
AR050383	ARDLIE, KRISTIN G	GENOMICS COLLABORATIVE, INC.	OSTEOPOROSIS CANDIDATE GENES: IN SILICO AIDED DISCOVERY
AR047869	BLUM, MIRIAM	TUFTS UNIVERSITY BOSTON	ROLE OF ADIPOSE TISSUE IN VITAMIN D METABOLISM
AR035582	CAULEY, JANE A	UNIVERSITY OF PITTSBURGH AT PITTSBURGH	STUDY OF OSTEOPOROTIC FRACTURES
AR049411	CHEN, ZHAO	UNIVERSITY OF ARIZONA	LONGITUDINAL CHANGES IN HIP GEOMETRY AND SKELETAL MUSCLE
AR048919	CUMMINGS, STEVEN R	CALIFORNIA PACIFIC MED CTR-PACIFIC CAMP	WHI SEX HORMONE & GENETIC RISK FACTORS FOR HIP FRACTURE
AR045614	ENSRUD, KRISTINE E	UNIVERSITY OF MINNESOTA TWIN CITIES	OSTEOPOROTIC FRACTURES IN MEN
AR002161	GREEN, REBECCA P	WASHINGTON UNIVERSITY	PREVENTION OF STERIOD INDUCED OSTEOPOROSIS IN CHILDREN
AR048846	HEANEY, ROBERT P	CREIGHTON UNIVERSITY	BONE-SPARING BY CA SALTS WITH & WITHOUT EXTRA PHOSPHORUS

AR035583	HILLIER, TERESA A	KAISER FOUNDATION RESEARCH INSTITUTE	STUDY OF OSTEOPOROTIC FRACTURES
AR035584	HOCHBERG, MARC C.	UNIVERSITY OF MARYLAND BALT PROF SCHOOL	STUDY OF OSTEOPOROTIC FRACTURES
AR050066	KARASIK, DAVID	HEBREW REHABILITATION CENTER FOR AGED	GENETICS OF BONE STRUCTURAL GEOMETRY: FRAMINGHAM COHORTS
AR049439	LAU, EDITH MC	CHINESE UNIVERSITY OF HONG KONG	OSTEOPOROTIC FRACTURES IN CHINESE MEN: MROS HONG KONG
AR048932	LEVIS, SILVINA	UNIVERSITY OF MIAMI-MEDICAL	BONE SPARING EFFECTS OF SOY PHYTOESTROGENS IN MENOPAUSE
AR045632	LEWIS, CORA ELIZABETH	UNIVERSITY OF ALABAMA AT BIRMINGHAM	OSTEOPOROTIC FRACTURES IN MEN (MR.OS)
AR047932	MILLIKEN, LAURA A	UNIVERSITY OF MASSACHUSETTS BOSTON	FACTORS AFFECTING THE BONE RESPONSE AND NON-RESPONSE
AR050450	ORCHARD, PAUL J	UNIVERSITY OF MINNESOTA TWIN CITIES	FIRST INTERNATIONAL SYMPOSIUM ON OSTEOPETROSIS:
AR045647	ORWOLL, ERIC S.	OREGON HEALTH & SCIENCE UNIVERSITY	OSTEOPOROTIC FRACTURES IN MEN (MR.OS)
AG022326	PEREIRA-SMITH, OLIVIA M	GERONTOLOGICAL SOCIETY OF AMERICA	CONFERENCE--BIOLOGY OF AGING
AR048616	SOLOMON, DANIEL H	BRIGHAM AND WOMEN'S HOSPITAL	RANDOMIZED CONTROLLED TESTING OF OSTEOPOROSIS EDUCATION
AR047852	SPECKER, BONNY L	SOUTH DAKOTA STATE UNIVERSITY	BONE DENSITY AND LATER BONE LOSS IN RURAL POPULATIONS
AR045583	STEFANICK, MARCIA L	STANFORD UNIVERSITY	OSTEOPOROSIS IN MEN

AR049401	VILLAREAL, REINA C	BARNES-JEWISH HOSPITAL	CYP GENE POLYMORPHISM AND ESTROGEN STATUS IN THE ELDERLY
AR049747	ZMUDA, JOSEPH M	UNIVERSITY OF PITTSBURGH AT PITTSBURGH	EPIDEMIOLOGY OF BONE LOSS IN AFRICAN MEN
AR050107	ZMUDA, JOSEPH M	UNIVERSITY OF PITTSBURGH AT PITTSBURGH	DETERMINANTS OF BONE STRENGTH IN AFRO-CARIBBEAN FAMILIES

National Institute of Child Health and Human Development

(NICHD)

THE NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT (NICHD)

Research Related to The Menopausal Transition
(Report of the NIH Office of Research on Women's Health and the Coordinating Committee on Research on Women's Health)

The NICHD has a unique role to play in women's health research. Although the Institute's mission is to ensure that babies are born wanted, timely, and healthy and that they develop to their full physical, emotional, and cognitive potentials, NICHD-sponsored research spans human growth and development. Given its mission, the NICHD portfolio includes a broad array of behavioral, basic, and clinical research on women's reproductive health, including studies related to menopause, to conditions that may be associated with physiological changes that lead to or occur in menopause, and to issues that may be related to hormone replacement therapy. Highlighted here are just some of the Institute's newest research projects related to menopause.

NICHD-supported researchers are examining some of the behavioral aspects related to menopause. For instance, to improve communication between healthcare providers and diverse groups of women about menopause and treatment recommendations, researchers are interviewing Latin, African-American, Japanese-American, and white women about their own understandings of menopause. The findings will allow researchers to develop culturally-sensitive interventions that may help healthcare providers to better communicate medical information about menopause to their patients.

In addition to behavioral research, the Institute supports basic research related to menopause. For instance, researchers are examining how menopause changes vaginal connective tissue and weak tissues that can result in pelvic organ prolapse. In the same study, the researchers will also examine whether hormone therapy in postmenopausal women improves the structural deficiencies in the vaginal connective tissue compared to postmenopausal women who are not taking a hormone therapy.

NICHD-supported researchers are also conducting a pilot study to test whether the drug, gabapentin, could be an effective treatment for hot flashes. The preliminary findings from this study may enable the researchers to design a full-scale randomized trial to test the effectiveness of this potential new drug. The findings from this and from all of the studies highlighted here may help researchers to develop methods to better treat and prevent menopausal symptoms and disorders related to aging, improving the quality of life for women.

NICHD Menopause-related Research: 2004

Project Number	Title	Investigator's Name	Institution
K08HD001463	THE ROLE OF ESTROGEN IN BONE METABOLISM	OZ, ORHAN K	UNIVERSITY OF TEXAS SW MED CTR/DALLAS
K23HD044729	Bridging Menopause: Experiences/Clinical Encounters	HILL-SAKURAI, LAURA E	UNIVERSITY OF CALIFORNIA SAN FRANCISCO
K24HD001290	NEUROENDOCRINE CONTROL OF REPRODUCTION IN THE FEMALE	HALL, JANET E	MASSACHUSETTS GENERAL HOSPITAL
R01HD038673	MODEL FOR PELVIC FLOOR DISORDERS	CLARK, AMANDA L	OREGON HEALTH & SCIENCE UNIVERSITY
R01HD038679	MECHANISMS OF INCONTINENCE FOLLOWING VAGINAL DISTENSION	DAMASER, MARGOT S.	LOYOLA UNIVERSITY CHICAGO
R01HD041131	Natural History of POP-- A Prospective Cohort Study	NYGAARD, INGRID E	NIVERSITY OF IOWA
R01HD043355	Estrogen Receptor Variance and CHD Risk in HERS	HERRINGTON, DAVID M	WAKE FOREST UNIVERSITY HEALTH SCIENCES
R01HD045590	IMPACT OF MENOPAUSE ON VAGINAL CONNECTIVE TISSUE SUPPORT	MOALLI, PAMELA A	MAGEE-WOMEN'S HEALTH CORPORATION
R03HD042609	Gabapentin vs Estrogen for the Treatment of Hot Flushes	REDDY, SIREESHA	UNIVERSITY OF ROCHESTER
U54HD041748	TESTOSTERONE RESPONSE IN SURGICALLY MENOPAUSAL WOMEN	DHASIN, SHALENDER	CHARLES R. DREW UNIVERSITY OF MED & SCI
Z01HD000628	REGULATION OF GROWTH AND REPRODUCTION	BONDY, CAROLYN A	NICHD
Z01HD000633	OVARIAN FOLLICULOGENESIS	NELSON, LAWRENCE M	NICHD

National Institute on Deafness and Other Communication Disorders (NIDCD)

National Institute on Deafness & Other Communication Disorders

Menopause Related Grants

Title	Grant Number	Principal Investigator	Institutition
GENES INVOLVED IN THE DEVELOPMENT OF VESTIBULAR OTOCONIA	R01DC02236-09	ORNITZ, DAVID M	WASHINGTON UNIVERSITY, ST. LOUIS

The vestibular organs of the inner ear include the otolith organs, used for detecting gravity and linear acceleration, which are important for postural and locomotor control. These organs are small pouches containing a matrix of dense calcified crystals called otoconia, imbedded in a proteinaceous matrix. Functional deficits in the vestibular system can lead to sensations of dizziness and vertigo, postural instability, and falling or vehicular accidents that can have serious medical consequences. Problems with balance are a leading cause of death and injury in elderly populations.

The project headed by Dr. Ornitz investigates the mechanisms by which the otoconia are formed, using mutant mouse models to identify genes that are expressed in the mammalian vestibular system during the development of the otoconia. Progress thus far has identified mutations in a new gene named otopetrin, showing its apparent requirement for correct otoconial development, and compared two proteins called Oc90 and Oc22 that are important for forming the protein matrix. These studies will provide molecular and biochemical tools to clarify the formation and turnover of otoconia. Human otoconia undergo changes involved with aging, compounded by potential problems related to changes in calcium metabolism, such as those related to bone degeneration in osteoporosis. This combination is particularly important in post-menopausal women, if aging vestibular dysfunction results in increased susceptibility for falls, with the potential for bone fracture injuries. Having a genetic tool for otoconial development gives some promise for restoring losses of otoconial structure and function.

National Institute of Dental and Craniofacial Research

(NIDCR)

National Institute of Dental and Craniofacial Research

The mission of the National Institute of Dental and Craniofacial Research (NIDCR) is to improve oral dental and craniofacial health through research, research training and the dissemination of health information. The Institute supports research in areas such as acquired and congenital conditions, infectious diseases (periodontal diseases and dental caries), oral cancers, oral manifestations of HIV infections, chronic and disabling disorders such as bone and joint diseases, and neurological and neurosensory disorders with emphasis on chronic pain. Research advances affecting women can be found within a number of these broad research categories.

Menopause Related Research

Role of Serotonin in Osteoclast Differentiation: The goal of this project is to identify and characterize the interactions between the neuroendocrine and skeletal systems. Recently, investigators reported that serotonin, a well-established neurotransmitter, regulates the activities of osteoclasts, which are bone-resorbing cells. Deregulation of the serotoninergic system leads to depressive disorders and other psychological disturbances. In the U.S., twice as many women as men are affected by a depressive disorder each year. This study suggests that serotoninergic disorders may be associated with changes in bone mass. This study also indicates that commonly prescribed anti-depressants that target the serotoninergic system, e.g. Prozac, may affect bone health and could be exacerbated in perimenopausal women.

Low-Dose Doxycycline Effects On Osteopenic Bone Loss: The objective of this study is to assess the clinical efficacy of low-dose doxycycline therapy in reducing bone loss caused by periodontitis and estrogen deficiency in postmenopausal women. The study is a 5-year, double-blinded randomized controlled trial using a placebo. Clinical measurements of periodontal disease and oral bone loss include probing depths, gingival attachment level and crevicular fluid. In addition, the systemic effect of low-dose doxycycline will be evaluated by dual-energy x-ray absorptiometry of the lumbar spine and femoral neck, and on serum and urine biochemical markers of bone turnover. Recruitment of 128 eligible women was completed in December 2003, and 118 are under active follow-up. Follow-up will be completed in late 2005 with results in presentations and publications in 2006. No serious adverse events have been reported.

Bone Mineral Density as a Predictor of Periodontitis: The overall goal of this study is to determine the role of oral and systemic bone mineral density (BMD) in the development of new and progressive periodontal disease in postmenopausal women. Two specific aims are to determine if low BMD at specific sites such as the mandible is linked to increased susceptibility of tooth loss**.** The study participants are a cohort of postmenopausal women enrolled in the Women's Health Initiative (WHI) who participated in a cross-sectional study that obtained baseline periodontal data. Participants will be followed for three years to assess the temporal relationship between BMD and periodontitis. The study completed its second year and is actively enrolling women. They have enrolled and completed data collection on 448 women. Their target is to enroll 1000 subjects from a total of 1348 eligible postmenopausal women.

Salivary Biomarkers to Predict Alveolar Bone Loss: The goal of this study is to develop an objective, rapid system that can be used with ease in the dental office to identify patients at high

risk for future alveolar bone loss. This information will allow the practitioner to target appropriate interventions to patients in most need of treatment and avoid expensive and time consuming treatment for patients having limited need for these services. The study will use an established method that uses paramagnetic microspheres coated with specific antibodies to capture, retrieve, concentrate and identify biomarkers associated with periodontal bone destruction in saliva. Additionally, the study will use this technology to also concentrate products of bone destruction, such as C-telopeptide pyridinoline crosslinks of Type I collagen (ICTP), osteocalcin and osteonectin from human saliva. These concentrated products will then be quantitated using simple colorometric methods. These biomarkers, all of which have been previously reported to be elevated in gingival crevicular fluid (GCF) of subjects with active periodontal disease, in conjunction with other well known risk factors, e.g. age, tobacco use, etc., will be used to develop statistical diagnostic models for predicting future alveolar bone loss, monitoring patients longitudinally with respect to any periodontal disease status change and evaluating treatment success or failure. Saliva, unlike GCF, is readily accessible and can be rapidly collected with minimal effort. Thus, this approach could be conveniently adapted in the future for use by practicing dentists to provide objective information to assess risk for periodontal bone loss.

National Institute of Dental and Craniofacial Research Menopause Related Project

Contract or Grant Number	Title	Principal Investigator	Institutions
R01 DE007378	Role of Serotonin in Osteoclast Differentiation	Stashencko, Philip P	Forsyth Institute
R01 DE012872	Low-Dose Doxycycline Effects On Osteopenic Bone Loss	Payne, Jeffrey B	University of Nebraska Medical Center
R01 DE013505	Bone Mineral Density as a Predictor of Periodontitis	Wactawski-Wende, Jean	State University of New York At Buffalo
R21 DE015854	Salivary Biomarkers to predict Alveolar Bone Loss	Scannapieco, Frank	State University of New York at Buffalo

National Institute of Diabetes and Digestive and Kidney Diseases

(NIDDK)

National Institute of Diabetes and Digestive and Kidney Diseases

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports research on a wide array of diseases and disorders that affect normal metabolism and/or organ development and function. These include diabetes, inborn errors of metabolism, endocrine disorders, osteoporosis, digestive diseases, obesity, nutritional disorders, hematological diseases, and urologic and renal diseases. Determining how and the extent to which menopause uniquely influences the onset or course of metabolic disorders and other diseases is important for developing appropriate prevention and treatment strategies for these conditions in women; equally important are ongoing efforts to prevent or treat those conditions for which menopause is a known or apparent "risk factor." Menopause is marked by dramatic changes in levels of gonadal, hypothalamic, and pituitary hormones, which have significant downstream physiological effects. Menopause is accompanied by loss of bone calcium, alterations in serum lipids resulting in a more atherogenic lipid profile, urogenital atrophy, and redistribution of body fat mass. These physiological changes are associated, respectively, with a rapid increase in risk for osteoporosis and cardiovascular disease--especially coronary heart disease--and may contribute to the increased prevalence of conditions such as urinary incontinence and the metabolic syndrome in postmenopausal women. The NIDDK supports basic and clinical research relevant to menopause in several areas, including diabetes, obesity and weight regulation, endocrinology, osteoporosis, and urologic disorders. The following are examples of recently completed or ongoing research relevant to menopause supported by the NIDDK.

Diabetes

Diabetes Prevention Program Outcomes Study (DPPOS): The Diabetes Prevention Program was the first major clinical trial in the U.S. to show that moderate changes in diet and exercise can delay and possibly prevent type 2 diabetes in a diverse population of overweight people with impaired glucose tolerance (a condition in which blood glucose levels are higher than normal but not yet diabetic). The DPP enrolled more than 3,200 participants--68 percent of whom are women and 45 percent of whom are from minority groups. The DPP found that modest weight loss--5 to 7 percent of body weight--and increased physical activity can cut a person's risk of developing type 2 diabetes by more than half. The DPP also found that the oral diabetes drug metformin (Glucophage®) reduces type 2 diabetes risk, although not as effectively as lifestyle changes. The lifestyle intervention worked equally well in men and women and in all the racial/ethnic groups represented in the study. A long-term follow-up study to the DPP, the DPP Outcomes Study (DPPOS) is examining the longer-term effects of the trial intervention on the development of type 2 diabetes and its complications, particularly cardiovascular disease, in DPP participants. It will also compare outcomes for women and men, and by age and ethnicity. Other associated health outcomes have been examined in the DPP participants; for example, emerging results indicate that the DPP lifestyle intervention had a positive effect on reducing prevalence of urinary incontinence in women[4]. The long-term effects of the DPP interventions on UI and other associated health outcomes will examined in the DPPOS, as well.

Genetic and Biochemical Predictors of Type 2 Diabetes Mellitus in Women: Diabetes mellitus is

[4] American Diabetes Association 64th Scientific Session, June 4-8, 2004, abstract 983-P.

a major and increasing public health problem, affecting an estimated 18.2 million Americans, of whom 90 to 95 percent have type 2 diabetes[5]. A novel hypothesis implicates inflammation and endothelial dysfunction in the pathogenesis of type 2 diabetes. Researchers are studying the role of several novel and promising biomarkers of inflammation and endothelial dysfunction as predictors of risk of type 2 diabetes. In addition, the pathogenic roles of specific genetic markers associated with inflammation and endothelial dysfunction are being studied. Elucidation of interrelationships between these biomarkers and development of type 2 diabetes may suggest new treatment and/or prevention strategies. This study will use samples from 4,300 ethnically diverse postmenopausal women free of cardiovascular disease or type 2 DM who are participating in the Women's Health Initiative Observational Study Cohort. It will include genetic analyses and comparison of data from different ethnic groups in order to improve understanding of genetic predictors for future risk of type 2 diabetes in different populations. Findings from this and similar studies could shed new light on the etiology of type 2 diabetes, especially among minority Americans such as Hispanic/Latinos, Blacks/Africans, and Asians/Pacific Islanders who bear a disproportionately high burden of this disease but for whom less data is available. (LIU, SIMIN R01 DK062290)

Estrogens and Insulin Resistance in Women: Estrogen status in premenopausal women may protect against fat-induced insulin resistance. This study will use two different approaches to test the hypothesis that men and non-hormonally-replaced postmenopausal women are vulnerable to fat-induced insulin resistance, while adequately estrogenized women are protected. The investigators will also conduct studies with both human participants and mouse models to determine whether estrogenization protects women from the insulin resistance induced by obesity and aging, including experiments aimed at identifying cellular mechanisms for these protective effects of estrogens. The investigators will also seek to determine whether the fat cell secreted protein ACRP3O (adiponectin) is modulated by estrogen status, and whether the insulin sensitizing effects of ACRP3O are responsible for the estrogen induced protection from insulin resistance. Findings from these studies could have significant implications concerning the mechanisms of insulin resistance as well as the treatment and possibly prevention of this disorder. (OLEFSKY, JERROLD R01 DK061964)

Complications of Diabetes

Cardiac Risk Factors in Hispanics with Type 2 Diabetes: Cardiovascular disease (CVD) is the most common cause of both morbidity and mortality in people with type 2 diabetes. Diabetic women have been shown to have a comparable incidence of CVD mortality with diabetic men, regardless of age. Apparently, the "protective" effects of estrogen observed in non-diabetic women are not observed in diabetic women. Hispanics have shown an increasing incidence rate of CVD that is nearly all accounted for by diabetes. Hispanic women with poorly controlled type 2 diabetes have been found to have a more atherogenic lipid profile than Hispanic diabetic and non-diabetic men. If close control of blood glucose restores the gender differences in CVD risk factors, this study could have great implications regarding the treatment of diabetic women. (AVILES-SANTA, MAINES K08 DK02606)

Obesity

[5] National Institute of Diabetes and Digestive and Kidney Diseases. National Diabetes Statistics fact sheet: general information and national estimates on diabetes in the United States, 2003. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, 2003. Rev. ed. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, 2004. http://diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm.

Menopause Effect on Obesity, Energy Balance and Insulin: Menopause has been associated with changes in body composition and increased cardiovascular risk factors in Caucasian women, although less information is available on the effects of menopause in African American women. The overall goal of this continuing longitudinal study, the Healthy Transitions Study, is to assess the influence of menopause on body composition and fat distribution, and to determine mechanisms that may influence body fat changes, in a cohort of Caucasian and African American women. Because health statistics for African American women are significantly worse than for the U.S. Caucasian population, understanding the effects of menopause on risk factors in African American women is of great public health significance. The researchers have reported on data from this study indicating that ethnic differences in energy expenditure and the intake of certain nutrients may influence the effect of menopausal transition on obesity in African American women[6]. (SMITH, STEVEN R01 DK050736)

Gender, Obesity, C-Reactive Protein, and Oxidative Stress: C-reactive protein (CRP), a marker of inflammation, is associated with cardiovascular disease, as well as with diabetes and other conditions. This study intends to investigate the hypothesis that some of the harmful effects of obesity, and of postmenopausal status, are attributable to fat-induced increases in CRP and lipid peroxidation. It will test, in a randomized, placebo-controlled trial, whether antioxidant supplements can lower CRP levels and reduce tissue damage from lipid peroxidation in nonsmokers; whether one antioxidant is significantly more effective than the other; whether treatment effects differ by gender or body fat; whether there are gender or body fat differences in baseline CRP or in baseline lipid peroxidation, in nonsmokers, independent of other covariates; and, in women, whether postmenopausal status is associated with higher baseline CRP or lipid peroxidation, after control of covariates. (BLOCK, GLADYS R01 DK062378)

Sex Steroid, HPA Regulation, and Fat Patterning: Central (visceral) obesity contributes to an excess risk of diabetes, dyslipidemia, and death from coronary heart disease in women. Women typically express central obesity during menopause but the mechanisms causing this change in fat distribution are poorly understood. This investigator has been investigating a possible role for estrogen regulation of the hypothalamic-pituitary-adrenal (HPA) axis in the expression of visceral obesity in postmenopausal women. One aim of this study is to complete a pilot study and to test the ability of estrogen to decrease HPA activity and cortisol levels on a prospective basis in postmenopausal women. These studies will provide pilot data for studies of estrogen regulation of the HPA axis activity and subsequent changes in body fat distribution in women transitioning through the menopause. (PURNELL, JONATHAN R03 DK061996)

Look AHEAD (Action for Health in Diabetes): This multicenter, randomized clinical trial will examine the effects of a lifestyle intervention program designed to promote weight loss through reduced calorie intake and regular exercise in 5,145 volunteers. Look AHEAD will examine how the lifestyle intervention affects heart attack, stroke, and cardiovascular-related death in people with type 2 diabetes--the disease most affected by overweight and obesity. The study will recruit individuals between 45 and 75 years of age with type 2 diabetes, who are classified as overweight or obese. Women comprise 59.4 percent of participants and at least one third of the participants are from racial and ethnic minority groups in the United States. Look AHEAD is collecting self-report data on women's health, including questions about history of pregnancies, use of hormone medication, and menopausal status. Other sponsoring institutes and

[6] Lovejoy JC, Champagne CM, Smith SR, de Jonge L, and Xie H. Ethnic differences in dietary intakes, physical activity, and energy expenditure in middle-aged, premenopausal women: the Healthy Transitions Study. *Am J Clin Nutr*. 74:90-5, 2001.

organizations for Look AHEAD include the National Heart, Lung, and Blood Institute (NHLBI), National Institute of Nursing Research (NINR), the ORWH, the National Center for Minority Health and Health Disparities (NCMHD), and the Centers for Disease Control and Prevention (CDC).
http://www.niddk.nih.gov/patient/SHOW/lookahead.htm

Endocrinology

Pathogenesis and Therapy of Autoimmune Thyroid Disease: Autoimmune thyroid disease (AITD) affects at least six percent of all women in their lifetime, and more than ten percent of older women. This research program aims to understand the causes of human autoimmune thyroid disease, the mechanisms involved in controlling the immune response, and if possible, to develop preventive or therapeutic measures based on the immunology of the disease. (DEGROOT, LESLIE J. R01 DK027384)

Menopause, IDDM and Autoimmunity--The FAD Study: The Familial Autoimmune and Diabetes (FAD) Study has shown that the prevalence of Hashimoto's thyroiditis is higher among adult women with type 1 diabetes than their non-diabetic sisters or mothers. These findings suggest that one's ability to maintain immunological self-tolerance may be lost prematurely among women with type 1 diabetes. This may also reflect one of the many chronic complications that occur at an early age among affected individuals. It is expected that other indicators of advanced biological age may be common among women with type 1 diabetes. Self-report data from the FAD study supports this hypothesis. The mean age at menopause for women with type 1 diabetes was nearly ten years younger than that for their non-diabetic sisters. This appears to be the first formal report of an association between type 1 diabetes and early menopause in the literature. Moreover, the public health importance of these data, which must be confirmed, is enormous. Given the high incidence of cardiovascular disease and other complications known to be associated with long-term diabetes, an early natural menopause is likely to exacerbate the risk of myocardial infarction among young women with type 1 diabetes. This study will validate the extremely important finding that menopause occurs at a significantly younger age among type 1 diabetic women when compared to non-diabetic women. It will also evaluate the potential differences in menstrual bleeding patterns, menopausal symptomatology and the determinants of age at menopause among type 1 diabetic compared to non-diabetic women. In addition, the study will evaluate the effect of the menopause transition on major cardiovascular disease risk factors and risk of autoimmune thyroid disease among type 1 diabetic compared to non-diabetic women. These researchers recently reported the first set of natural history data for the menstrual cycle across all ages of women with type 1 diabetes, which reveals a significant increase in menstrual cycle disturbances before age 30 in these women[7]. (DORMAN, JANICE S. R01 DK044590)

Bone Loss and Osteoporosis

Pathophysiology of PTH-related Protein (1-36) in Humans: Current treatments for osteoporosis focus almost exclusively on agents that inhibit bone resorption. PTH mediates bone formation as well as bone resorption, and in clinical studies has shown promise as an osteoporosis treatment. Recent studies have demonstrated that human parathyroid hormone-related protein (PTHrP(1-

[7] Strotmeyer ES, Steenkiste AR, Foley TP Jr, Berga SL, and Dorman JS. Menstrual cycle differences between women with type 1 diabetes and women without diabetes. *Diabetes Care* 26:1016-21, 2003.

36)) has many properties similar to PTH, can be safely administered to humans. Results from a Phase II clinical trial conducted through this project suggest that PTHrP is a pure anabolic agent for the treatment of postmenopausal osteoporosis when administered to women on estrogen therapy[8]. The overall goal of this study is to determine whether PTHrP(1-36) is indeed a potent anabolic skeletal agent in humans, if its anabolic effects are maintained in the absence of estrogen supplementation, and if it is similar to, or perhaps superior to, PTH in the treatment of osteoporosis. Findings from these studies could result in a better understanding of the therapeutic potential of PTHrP(1-36). (STEWART, ANDREW F. R01 DK051081)

Vitamin K and Bone Turnover in Postmenopausal Women: Accumulating data suggest that vitamin K (K) insufficiency may contribute to osteoporosis development by causing by causing increased bone turnover. However, currently available data do not permit definitive conclusions to be drawn regarding a role of K in bone metabolism. The goal of this study is to clarify the role of K insufficiency in skeletal health through a prospective, randomized, double-blind, placebo controlled trial of K1 supplementation in 226 postmenopausal women. Several measures of skeletal turnover will be used to assess the effect of K supplementation on this phenomenon. Findings from this study could help inform recommendations for K supplementation as part of measures to prevent osteoporosis. (BINKLEY, NEIL C. R01 DK058363)

Urinary Tract Health

Risk Factors for Urinary Tract Infections in Postmenopausal Women: Urinary tract infections (UTI) are one of the most common infections in women. Research on the epidemiology and etiology of UTI has concentrated on two groups of women--the young and healthy and the elderly and debilitated. In elderly women, general debility, voiding problems, diabetes, and possibly estrogen deficiency are risk factors. Less is known about risk factors for UTI in women soon after menopause. This project has been prospectively evaluating the incidence of acute UTI and assessing risk factors for this problem in a cohort of postmenopausal women. The primary aims of the study have been to learn the relative effects of diabetes, postmenopausal estrogens, urinary incontinence or increased post-void residual urine, and sexual activity on the risk of UTI. Recent reports from this group have provided insights into the significance of treated diabetes--particularly insulin-treated diabetes or diabetes of long duration--history of UTI, and urinary incontinence as risk factors for UTIs in healthy postmenopausal women (aged 55 to 75)[9]. Another study using this cohort (*H_2O_2-Producing Lactobacilli And Postmenopausal UTI*) has been examining whether changes in the vaginal bacterial flora predispose to UTI in postmenopausal women and how various factors, such as diabetes and estrogen therapy, affect the vaginal flora. A report on these interrelationships has recently been published[10]. (FIHN, STEPHAN D. R01 DK041341; GUPTA, KALPANA K23 DK2660)

Risk Factors for Urinary Incontinence in Women: This study has been capitalizing on the availability of two large prospective studies of women aged 37-85 years, to examine the epidemiology of urinary incontinence (UI) across varying age groups. The investigators have

[8] Horwitz MJ, Tedesco MB, Gundberg C, Garcia-Ocana A, and Stewart AF: J Clin Endocrinol Metab 88: 569-75, 2003

[9] Jackson SL, Boyko EJ, Scholes D, Abraham L, Gupta K, and Fihn SD: Predictors of urinary tract infection after menopause: a prospective study. Am J Med. 2004 Dec 15;117(12):903-11.
Hu KK, Boyko EJ, Scholes D, Normand E, Chen CL, Grafton J, and Fihn SD: Risk factors for urinary tract infections in postmenopausal women. Arch Intern Med. 2004 May 10;164(9):989-93

[10] Pabich WL, Fihn SD, Stamm WE, Scholes D, Boyko EJ, and Gupta K: Prevalence and determinants of vaginal flora alterations in postmenopausal women. J Infect Dis. 2003 Oct 1;188(7):1054-8.

been examining prospectively, through comprehensive questionnaires, the relation of reproductive characteristics, menopause, body weight and physical activity, and hormonal factors to the incidence of UI, to different types of UI (urge, stress, or mixed incontinence), to its severity, its progression, and to its impact on women s daily lives. The investigation utilizes the Nurses Health Study and the Nurses Health Study II, observational studies of 121,701 and 116,678 female nurses, respectively. These two existing cohorts provide a cost-efficient basis for conducting a prospective study of UI, allowing better understanding of the epidemiology of UI, and identification of preventive strategies. In addition, the establishment of these cohorts for studying incontinence will allow future investigations of many other issues, such as the effect of diet and various lifestyle habits. The group has recently reported that, in a cohort of nearly 40,000 participants from the NHS I and II, postmenopausal hormone therapy (irrespective of type or route of administration) appears to increase the risk of developing UI[11]. (GRODSTEIN, FRANCINE R01 DK062438)

Urinary Incontinence Treatment Network (UITN): In community dwelling adults, urinary incontinence affects an estimated 35 percent of women 65 years or older and 10 percent of women younger than 65 years[12]. Urinary incontinence, which affects mostly women, is a problem often associated with pregnancy, childbirth, menopause, and aging. The UITN was established in 1999 in collaboration with the NICHD and with support from the ORWH. The purpose of the UITN is to establish a group of collaborating investigators who will conduct long-term studies, including clinical trials, of the most commonly used surgical, pharmacological, and behavioral approaches to the management of urinary incontinence in women diagnosed with stress and mixed incontinence. The first protocol implemented by the UITN is a randomized controlled clinical trial of two surgical procedures commonly used to treat women with stress urinary incontinence, the sling and Burch procedures. This ongoing study and other assessments will provide both physicians and patients with important information necessary to make well-informed decisions about the best treatment options. The UITN is currently enrolling patients for a second trial, which will focus on treating women with pure or predominantly urge incontinence.
http://www.niddk.nih.gov/patient/uitn/uitn.htm

[11] Grodstein F, Lifford K, Resnick NM, and Curhan GC. Postmenopausal hormone therapy and risk of developing urinary incontinence. Obstet Gynecol. 2004 Feb;103(2):254-60.
[12] Wilson L, Brown JS, Shin GP, Luc KO, and Subak LL. Annual Direct Cost of Urinary Incontinence. Obstetrics and Gynecology. 2001;98:398-406.

National Institute on Drug Abuse

(NIDA)

National Institute on Drug Abuse

Grant Portfolio on Menopause, Aging Women, and Hormone Therapy

1. ADRIAN DOBS, PI

Grant Number: R01DA14098-05

Grant Title: Cognitive Consequences of Endocrine Dysfunction in IDUs

Purpose: The study will determine the relationship between gonadal milieu and quality of life in IDUs infected with HIV; patterns of cognitive performance and QOL; evaluate the safety and efficacy of sex hormones replacement therapy on cognitive performance and QOL in men and women.

Publications: Research suggests that endogenous sex hormones play an important role in regulating lipid metabolism in postmenopausal women (Mudali et al. J Clin Endocrinol Metab, 2005, 90(2): 1202-1209); that there is a reduced bone mineral density in HIV-infected patients and is associated with increased central adiposity and postload hyperglycemia (Brown et al. J. Clin Endocrinol Metab. 2004, 89(3): 1200-1206); and opiate use is a potential contributor to the endocrine and metabolic complications in HIV infection (Clin Infect Dis. 2003, 37 Suppl. 2, s132-6).

- Mudali S, Dobs AS, Ding J, Cauley JA, Szklo M, Golden SH. Endogenous postmenopausal hormones and serum lipids: the atherosclerosis risk in cummunities study. J. Clin Endocrinol Metab. 2005; 90(2):1202-9.
- Brown TT, Ruppe MD, Kassner R, Kumar P, Kehoe T, Dobs AS, Timpone J. Reduced bone mineral density in human immunodeficiency virus-infected patients and its association with increased central adiposity and postload hyperglycemia. J. Clin Endocrinol Metab. 2004; 89(3): 1200-6.
- Cooper OB, Brown TT, Dobs AS. Opiate drug use: a potential contributor to the endocrine and metabolic complications in human immunodeficiency virus disease. Clin Infect Dis. 2003; 37 suppl 2: s132-6.

2. ERNEST DRUCKER, PI

Grant Number RO1 DA11324

Title of Grant: Office-Based Methadone Prescribing

Purpose: This grant contains a menopause sub-study. Due to the aging of the heroin-dependent population, menopause affects many women in methadone treatment. Menopausal symptoms mimic some of the effects of narcotic withdrawal and are easily confused (by both former addicts and practitioners) with symptoms related to improper methadone dosage. Yet little attention is currently paid to menopausal care and it relationship to methadone dosing within methadone treatment. This sub-study is addressing that issue.

Publication:

Ellen Tuchman, E. (2004). Methadone and Menopause: Midlife Women in Drug Treatment, Journal of Social Work Practice in the Addictions, Vol.3(2), 44-55. [As a rising number of midlife women receive methadone treatment, issues related to the menopausal transition take on increased importance. The similarity between many of the symptoms associated with opiate withdrawal, methadone and menopause make it plausible these women and clinical staff attribute menopausal symptoms to other conditions of greater familiarity. The paucity of research, multiplicity of health problems and typically poor access to health care, further complicate the picture and underscore the importance of better integration of health care and social work intervention.]

3. JAMES E. FERGUSON, PI

Grant number: 5 K12 DA014040-05

Title of grant: Interdisciplinary Research Careers in Women's Health

Purpose: This program is designed to train junior faculty members ("Scholars") at University of Kentucky College of Medicine in interdisciplinary women's health research, and in encouraging their research endeavors. The grant is presently focused on 1) drug abuse and its relationship to sex and gender differences, 2) cancer as it relates to women's health, 3) hormonal regulation across a woman's lifespan, and 4) oral health and its impact on women's cardiovascular and endocrine (diabetes) health and on pregnancy outcomes. Program Scholar graduates and their projects include:

Publications:

- Dimayuga FO, Reed JL, Carnero GA, Wang C, Dimayuga ER, Dimayuga VM, Perger A, Wilson ME, Keller JN and Bruce-Keller AJ. Estrogen and Brain Inflammation: Effects on Microglial Cytokine Release and MHC/Co-stimulatory Molecule Expression. J Neuroimmunol 161:123-36, 2005). [Finding: Estrogen decreased components of adaptive immunity in cultured microglial cells]
- Wise PM, Smith MJ, Dubal DB, Wilson ME, Rau SW, Cashion AB, Bottner M and Rosewell KL. Neuroendocrine modulation and repercussion of female reproductive aging. Recent Prog Horm Res 57:235-56, 2002. [Finding: Age-related changes in the ability of estradiol to coordinate the neuroendocrine events that lead to regular preovulatory gonadotropin-releasing hormone surges contribute to the onset of irregular estrous cycles and eventually to acyclicity. Furthermore, the lack of estradiol increases the vulnerability of the brain to injury and neurodegeneration.]
- Wilson ME, Liu Y and Wise PM. Estradiol modulates anti-apoptotic signals in the cortical explant cultures. Brain Res Mol Brain Res 102:48-54, 2002. [Finding: Estradiol prevents injury-induced apoptosis, and activation of the serine/threonine protein kinase Akt may mediate these protective effects.]

4. ROBERT KLEIN, PI

Grant Number: 5R01DA14998

Grant Title: Atherosclerosis/Bone loss/Drug use/HIV in Older Men

Purpose: The PI is studying: (1) the effect of HIV infection and HAART on the rate and risk factors for atherosclerotic disease. Among the risk factors to be considered will be dyslipidemia insulin resistance obesity diet and medication and illicit drug and alcohol use; (2) determine the effect of HIV infection and HAART on age-related loss of bone mass; (3) determine the effect of HIV infection and HAART on high-risk drug using and sexual behaviors of older men. The PI will compare these observations with those in older women from their earlier study.

5. MAHENDRA KUMAR, PI

Grant Number: R01DA13550-01A2

Grant Title: HIV1 + IDU's--Endocrine Consequences and Medical Outcomes

Purpose: This study investigates the mediating role of endocrine consequences on the occurrence of mental health outcomes (depression, anxiety and perceived psychological distress) in HIV infected IDUs. They will investigate the responses of the thyroid and gonads to trophic hormones- thyroid releasing hormone (TRH) and luteinizing hormone-releasing hormone (LHRH) as well as adrenal activity in response to a low-dose ACTH challenge mainly in African-American and Hispanic men and women.

6. NANCY K. MELLO, PI

Grant Number: 5P01DA014528-4

Grant Title: Cocaine and Polydrug Abuse: New Medication Strategies

Purpose: The grant is concerned with cocaine's acute effects on the neuroendocrine system and how that contributes to its abuse liability. It includes four inter-related clinical and pre-clinical projects designed to facilitate medication development. It relates menopause, older women and/or hormone therapy only in that cocaine produces increases in estradiol, testosterone, and luteinizing hormone in monkeys with some gender differences. The magnitude of the changes in LH were dependent upon baseline differences in estradiol in females. Life cycle changes in hormonal milieu may determine the magnitude of hormonal responses to cocaine, which may be related in to its abuse liability and changes in menstrual cycle in females.

Publications:

- Mello et al., (2004) Effects of cocaine on gonadal steroid hormones and LH in male and female rhesus monkeys. Neuropsychopharm. 29: 2024-2034.
- Caine et al. (2004) Effect of gonadectomy and gonadal hormone replacement on cocaine self-administration in female and male rats. Neurpsychopharm 29: 929-942.
- Mello et al. (2004) Ovarian steroid hormone modulation of the acute effects of cocaine on luteinizing hormone and prolactin levels in orvariectomized rhesus monkeys. JPET 307-156-167.
- Negus et al., (2004) Sex differences in thermal nociception and prostaglandin-induced thermal hypersensitivity in rhesus monkeys J. Pain 5: 92-103.

7. JACK H. MENDELSON, PI

Grant Number: 5 R01 DA15067-03

Grant Title: Neurobiology of Nicotine: Hormones and Behavior

Purpose: This study is aimed at investigating the interactions between cigarette smoking and menstrual cycle phase. Preliminary data suggest that the subjective and endocrine effects of cigarette smoking are greater during the follicular than during the luteal phase of the menstrual cycle. A second study's findings suggest that menstrual cycle phase modulates the effects of cigarette smoking on mood states and neuroendocrine hormones in women.

Publications: No publications from this portion of the grant; however, there have been two presentations at scientific meetings:

- Mendelson, J.H., Sholar, M,B., Goletiani, N., Siegel, A.J. and Mello, N,K,. Comparison of the effects of cigarette smoking on the hypothalamic-pituitary-adrenal axis and prolactin in follicular phase women and men, College on Problems of Drug Dependence, San Juan, PR, 2004.
- Mendelson, J.H., Sholar, M,B., Goletiani, N., Siegel, A.J. and Mello, N,K,. Menstrual cycle phase influences the effects of cigarette smoking on mood states and the HPA axis. American College of Neuropsychopharmacology, San Juan, PR, 2004.

8. ELLIE SCHOENBAUM, PI

Grant Number: 5R01DA13564-01

Grant Title: Natural History of Menopause in HIV Infected Drug Users

Purpose: This study investigates the process of menopause among HIV-infected women and includes study of: (1) the impact of HIV infection and drug use on menopausal symptoms and biologic markers; (2) attitudes and knowledge about menopause among HIV infected and drug using women (3) the impact of H IV infection and drug use on bone mineral density before and after menopause:

and (4) impact of HIV infection and antiretroviral therapy (HAART) on dyslipidemia insulin resistance and development of post-menopausal cardiovascular disease.

9. MEHMET SOFUOGLU, PI

Grant Number: 5 R01 DA14537-02

Grant Title: Progesterone and the Effects of Nicotine

Purpose: The menstrual cycle phase may affect smoking behavior and the severity of tobacco withdrawal symptoms in female smokers. It has been observed that progesterone treatment may attenuate the subjective effects and craving for cigarettes. This is a double-blind, placebo-controlled study in which male and female smokers will be randomly assigned to one of the 3 treatment conditions: placebo, low (200 mg/day) or high dose (400 mg/day) of progesterone for four days. The investigators hypothesize that progesterone treatment, dose-dependently, will reduce smoking behavior, attenuate tobacco withdrawal symptoms, and subjective rewarding effects of smoking in both male and female smokers. This study may provide a better understanding of the mechanisms, which mediate the sex and menstrual cycle phase effects on nicotine dependence.

10. DANIEL SOLOMON, PI

Grant Number: 1R01DA15507

Grant Title: Pain Medication Use & Risk Factors for Opioid Dependence

Purpose: This grant will examine the extent and determinants of chronic prescription opioid use problems among Medicare patients who are diagnosed as having osteoarthritis or rheumatoid arthritis. Prescription opioid abuse will be examined in a community-based cohort of 250,000 Medicare patients who receive prescription drug benefits from the Pennsylvania Department of Aging's Pharmaceutical Assistance Contract for the Elderly (PACE). All eligible patients are over 65. The sample is 81% female.

Publications:

- Fischer MA, Schneeweiss S, Avorn J, Solomon DH. Medicaid prior-authorization programs and the use of cyclooxygenase-2 inhibitors. N Engl J Med. 2004 Nov 18;351(21):2187-94. BACKGROUND: Over the past five years, selective cyclooxygenase-2 inhibitors (coxibs) have accounted for a growing proportion of prescriptions for nonsteroidal antiinflammatory drugs (NSAIDs). To control these expenses, many state Medicaid programs have implemented prior-authorization requirements before coxibs can be prescribed. This study evaluated the effect of such programs on the use of coxibs by Medicaid beneficiaries. METHOD: Using data for all filled prescriptions in 50 state Medicaid programs from 1999 through the end of 2003, the researchers calculated the proportion of defined daily doses of NSAIDs accounted for by coxibs. Time-series analyses were used to measure the changes in prescription patterns after the implementation of each prior-authorization program. RESULTS: By 2001, coxibs accounted for half of all NSAID doses covered by Medicaid. This proportion varied widely according to the state in 2003, from a low of 11 percent to a high of 70 percent of all NSAID doses. Twenty-two states implemented prior-authorization programs for coxibs during the study period. Overall, the implementation of such programs reduced the proportion of NSAID doses made up by coxibs by 15.0 percent (95 percent confidence interval, 10.9 to 19.2 percent), corresponding to a decrease of 10.28 dollars (95 percent confidence interval, 7.56 dollars to 13.00 dollars) in spending per NSAID prescription.
- Solomon DH, Avorn J. Pharmacoepidemiology and rheumatic diseases: 2001-2002. Curr Opin Rheumatol. 2003 Mar;15(2):122-6. Pharmacoepidemiology is the branch of epidemiology that focuses on medications and their outcomes, including both adverse events and intended consequences. Such studies have become more prominent in rheumatology as the number of new medications has grown and prescribing databases have become more available. In the past year,

the potential cardiovascular complications associated with selective COX-2 inhibitors have become an important concern. A number of pooled analyses suggest the possibility of an increased risk of acute myocardial infarction, and studies of naproxen have found a possible protective effect. Accumulating evidence supports the contention that early initiation of disease modifying antirheumatid drug therapy improves outcomes of patients with rheumatoid arthritis. Open-label extensions of biologic therapies found continued benefits extending several years with the TNF-alpha antagonists, but concerns have arisen regarding tuberculosis and central nervous system demyelination with these agents. Data continue to be published quantifying the risk of osteoporosis associated with glucocorticoids, and the association between biphosphonate therapy and upper gastrointestinal events appears to be less of a concern that originally described.

National Institute of Environmental Health Sciences

(NIEHS)

NIEHS GRANTS RELATED TO MENOPAUSAL TRANSITION
FY2004

F32ES11941 Pru, James K. Massachusetts General Hospital
Control of Maternal-Fetal Interaction by PAS Genes

Abstract: The aryl hydrocarbon receptor (AHR), AHR nuclear translocator (ARNT) and hypoxia-inducing factor-la (HIF-l a) are members of the Per/Arnt/Sim (PAS) family of proteins that regulate transcription of target' genes in response to physiological (e.g., endogenous signals) and pathological (e.g., environmental toxicants) cues. Interestingly, PAS family members, including the AHR and ARNT, are constitutively expressed in many tissues, including those of the female reproductive system. Of relevance to this application, expression of the AHR and ARNT at uterine implantation sites (fetal and maternal interfaces), coupled with the fact that Ahr-deficient female mice have reduced litter sizes, suggest that the members of the PAS family have a biological function during pregnancy. Moreover, chemical Iigands of the AHR, such as polycyclic aromatic hydrocarbons (PAH) derived from the incomplete combustion of fossil fuels and tobacco smoke, have been implicated from both epidemiological and animal studies to have deleterious effects on pregnancy. Computer-based sequence analysis of a number of genes previously shown to be functionally required for the establishment of pregnancy and decidualization, in addition to novel genes regulated by the embryo (presented herein), has revealed that the promoters of many of these genes harbor AHR response elements. Such findings are in keeping with results from Dr. Tilly's lab using PAH-exposed ovaries in gene profiling experiments (microarrays), Which identified many of these same genes as being putative targets for the AHR. Based on these observations, it is hypothesized that PAS family members serve as key regulatory switches to coordinate the expression of specific genes in the uterus during pregnancy, both in response to the decidualization process and in response to an embryonic-derived factor(s). Of particular interest for consideration of PAS transactivation are the genes cylooxygenase-2, prostaglandin '2 synthase, peroxisome proliferator-activated receptor-□ and retinoic acid X receptor a (general decidualization process), and acid sphingomyelinase and interferon stimulated gene 15 (induced by the embryo). Furthermore, the candidate also hypothesizes that environmental toxicants, such as PAH, alter the expression of these genes in a manner incompatible with the establishment or maintenance of pregnancy. As such, results from the proposed experiments will not only shed new light on the role of PAS family members and their target genes in embryo implantation and pregnancy, but also how the magnitude and temporal aspects of this expression must be precisely coordinated for pregnancy to occur.

Publications:

Takai Y, Canning J, Perez GI, Pru JK, Schlezinger JJ, Sherr DH, Kolesnick RN, Yuan J, Flavell RA, Korsmeyer SJ, Tilly JL. Bax, caspase-2, and caspase-3 are required for ovarian follicle loss caused by 4-vinylcyclohexene diepoxide exposure of female mice in vivo. Endocrinology. 2003 Jan;144(1):69-74.

P30ES00002 Brain, Joseph D. Harvard School of Public Health
HSPH NIEHS Center for Environmental Health

Abstract: Our Center fosters active collaborations among three Research Cores: 1) Metals, 2) Urban and Occupational Particles, and 3) Organic Pollutants. The work of the Research Cores is greatly enhanced by three Facility Cores: 1) Biological Analyses, 2) Exposures and Environmental Analyses, and 3) Environmental Statistics. Finally, the investigators' ability to make their research and knowledge available to the public is greatly enhanced by the Community Outreach and Education Program (COEP). Other Center activities, such as pilot projects, new investigators, and program enrichment are catalytic mechanisms to achieve integration, interaction, productive, and innovative science. The objectives of this NIEHS Center are to generate new knowledge relating to the physiology, pharmacology, pathology, cell biology, molecular biology, genetics, and epidemiology of environmental disease, and to apply this knowledge to new modalities of prevention, diagnosis, and therapy. The investigators achieve these objectives through a variety of approaches, which range from studies of molecules and cells to those of whole animals and human populations. Through the organizational structure and financial support provided by the NIEHS Center Grant, the investigators' will increase the impact of their research and teaching in environmental health. In toto, the Harvard NIEHS Center for Environmental Health continues to be a major focal point for environmental research and training in Boston. The NIEHS Center mechanism enhances connections and makes the Harvard NIEHS Center part of a national and international network.

Publications:

Garrido Latorre F, Hernandez-Avila M, Tamayo Orozco J, Albores Medina CA, Aro A, Palazuelos E, Hu H. Relationship of blood and bone lead to menopause and bone mineral density among middle-age women in Mexico City. Environ Health Perspect. 2003 Apr;111(4):631-6.

P30ES06694 Liebler, Daniel C. University of Arizona
Southwest Environmental Health Sciences Center

Abstract: Through the NIEHS Center Core Grant Program the University of Arizona Center for Toxicology will develop the Southwest Environmental Health Sciences Center (SWEHSC), at the University of Arizona. The EHSC will be a major component of the University of Arizona Center for Toxicology, which was established by the Arizona Board of Regents in 1987. The mission of the EHSC is to integrate, coordinate and expand interactions among a group of established investigators conducting high quality research in the area of environmental health sciences. This mission will be fulfilled by fostering interdisciplinary approaches to understanding mechanisms by which environmental chemicals impact human health and to identifying factors that affect these mechanisms. Thirty-two SWEHSC Investigators have formed four interdisciplinary Research Programs that represent current research activities and provide the basis for new research initiatives. These Programs are Biotransformation, Metals, Cell Injury and Environmental Genetics. To increase productivity and enhance the quality of research being conducted in each of these Research Programs, three Service Cores (Synthetic Chemistry, Analytical Services, Experimental Pathology) have been formed. These cores will offer certain routine services and assist investigators in introducing new methodologies into their research. In addition to the three Service Cores, a Transgenic Animal Facility will be developed within the Environmental Genetics Research Program. The Administrative Core will provide enrichment programs for SWEHSC investigators through seminars and workshops, recruit new SWEHSC Investigators both from within and outside the University of Arizona, promote opportunities for innovative research ideas through the Pilot Projects Program, and oversee all activities. The Community Outreach and Education Program will encourage students, particularly minority

students to consider careers in environmental health; establish collaborative research and education programs in Mexico; and offer programs in environmental sciences to health related professionals. The SWEHSC will be a regional representative of NIEHS serving citizens in the Southwest. Because of the proximity of this area to Mexico and collaborative interactions to develop environmental health science programs in that country, SWEHSC will have a positive health impact on citizens on both sides of the border.

Publications:

Mayer LP, Pearsall NA, Christian PJ, Devine PJ, Payne CM, McCuskey MK, Marion SL, Sipes IG, Hoyer PB. Long-term effects of ovarian follicular depletion in rats by 4-vinylcyclohexene diepoxide. Reprod Toxicol. 2002 Nov-Dec;16(6):775-81.

P30ES07049 Peters, John M. University of Southern California
Environmental Exposures, Host Factors and Human Disease

Abstract: This application is to continue our Southern California Environmental Health Services Center whose main purposes are 1) to study the effects of environmental exposures on humans; 2) to determine host factors (genetic and other) influencing response to these exposures; and 3) to inform the public. To accomplish these goals we bring together an interdisciplinary team of investigators from 2 major Souther California universities: USC and UCLA. The research of our Center features interdisciplinary cornerstones: detained exposure assessment, including toxicokinetics and biomarkers; cutting edge study design, including the most powerful statistical and epidemiologic approaches; and the basic sciences, including physiology, molecular biology, genetics, chemistry and engineering. The foci of the Center cover a wide range of problems and address environmental exposures of public health importance including indoor and outdoor air pollution, pesticides, alflatoxins, radiation, passive smoking, bioaerosols and nitrites. The 5 Research Cores consist of: Respiratory Effects; Exposure Assessment; Childhood Cancer, Adult Cancer Study Design and Statistical Methodology. The 3 Facility Cores consist of: the Molecular Biology, Sample Processing and Storage Core; the Analytic Chemistry, Exposure Assessment and Aerosol Sciences Core; and the Biostatistics Core. The Center also features a separate core for Community Outreach and Education (COEP). The Center is structured to promote interdisciplinary research and linkage between the research and the COEP. Processes creating these interactions include the seminar series, pilot projects, research focus groups, workshops and retreats. The first 4 years of support for this Center have resulted in recruitment of new investigators, more investigators working on environmental health problems, doubling of funding support, more interaction between researchers from different disciplines and a greater production of research findings relevant to answering critical public health questions. The Center also developed research initiatives for the next 5 years that focus the interdisciplinary team of investigators on important environmental health problems involving genetic-environmental interactions as asthma and cancer.

Publications:

Ursin G, Tseng CC, Paganini-Hill A, Enger S, Wan PC, Formenti S, Pike MC, Ross RK. Does menopausal hormone replacement therapy interact with known factors to increase risk of breast cancer? J Clin Oncol. 2002 Feb 1;20(3):699-706.

Pike MC, Ross RK. Progestins and menopause: epidemiological studies of risks of endometrial and breast cancer. Steroids. 2000 Oct-Nov;65(10-11):659-64.

P30ES10126 Swenberg, James A. University of North Carolina at Chapel Hill
UNC-CH Center for Environmental Health & Susceptibility

Abstract: The focus of this "UNC-CH Center on Environmental Health and Susceptibility" is in the area of environmental epidemiology and toxicology. Three research cores will form the intellectual heart of the Center, organized around the following areas of concentration: Genetic Susceptibility, bringing together laboratory and molecular epidemiologic research on genomic determinants of susceptibility; Developmental Susceptibility, addressing the role of different stages in the life cycle and how these influence susceptibility to exposure, with a particular concentration on exposures received from conception through childhood; and Toxicokinetic Susceptibility, reexamining inter-individual variability in physiologic and metabolic factors that are responsible for the wide ranges in response to an exogenous agent. Four facility cores will provide critical services and will result in cost-efficiency for Center investigators: High Throughput Genotyping, Biostatistics and Epidemiologic Methods, Biomarkers, and Nutrient Assessment. The Administrative Core will have responsibility for coordination of Center activities, strategic planning and evaluation: the Pilot Projects Program; membership decisions; financial matters; leadership and visibility for UNC-CH's environmental health research. The Community Education and Outreach Program will assist the Administrative Core in dissemination and education about Center- related themes on environmental health to professionals, the media, and the public at large, with a focus on the state of North Carolina, and will promote two-way scientist/citizen interactions. This Center is designed to maximize cross-disciplinary integration to promote new research collaborations with exciting scientific potential, understand the mechanistic basis of chemical toxicity, and effectively reduce the burden of environmentally-related disease.

Publications:

Gaudet MM, Britton JA, Kabat GC, Steck-Scott S, Eng SM, Teitelbaum SL, Terry MB, Neugut AI, Gammon MD. Fruits, vegetables, and micronutrients in relation to breast cancer modified by menopause and hormone receptor status. Cancer Epidemiol Biomarkers Prev. 2004 Sep;13(9):1485-94

R01ES08430 Tilly, Jonathan L. Massachusetts General Hospital
Mechanisms of Aryl-Hydrocarbon-Induced Ovotoxicity

Abstract: Polycyclic aromatic hydrocarbons (PAH) are released into the environment by fossil fuel combustion. Another primary route of human exposure to PAH is cigarette smoke. Evidence that PAH cause premature ovarian failure has been provided by both epidemiological and animal studies. However, the mechanisms by which PAH damage the ovary have remained obscure for decades. These chemicals are particularly intriguing as there exists an intracellular binding protein for PAN termed the aryl hydrocarbon receptor (AHR). The AHR is a basic helix-loop-helix transcription factor that regulates gene expression following ligand interaction and nuclear translocation. During the previous funding cycle of this grant, the P1 completed experiments to validate the central hypothesis that PAN-mediated activation of the AHR in oocytes induces apoptosis by increasing expression of the gene encoding Bax, a pro-apoptotic member of the bcl-

2 gene family. However, several new questions arose during these studies. First, does the AHR function to set the "apoptosis susceptibility" of female germ cells by transcriptional regulation of cell death regulatory genes in addition to bax? Second, is the inability of dioxin, a known AHR ligand, to damage the ovary related to differences in AHR response element (AHRE) flanking sequences in "target" cell death regulatory genes (e.g., bax) that convey specificity for PAH-AHR versus dioxin-AHR interactions? Third, does the induction of bax gene expression in oocytes require an AHR-interacting protein(s) that permits AHR-bax gene promoter interaction? Based on preliminary data presented herein, the PT has hypothesized that PAH-AHR. but not dioxin-AHR, interaction transcriptionally sets the cell death susceptibility "rheostat" in female germ cells to favor apoptosis. This is accomplished via a coactivator(s) expressed in oocytes that facilitates functional interaction between the PAN-activated AHR and cell death regulatory gene promoters possessing AHRE. To test this hypothesis, the following Specific Aims are proposed for continuation of these studies: 1) to determine if expression of the pro-apoptotic bak gene is increased in oocytes exposed to PAN, if PAN-AHR interaction is required for increased transcriptional activity of the bak gene, and if expression of the endogenous bak gene is required for the ovotoxic effects of PAN; 2) to examine if the expression patterns of a number of key apoptosis regulatory genes, known to be expressed in oocytes, are altered by AHR deficiency and/or by PAH-driven AHR activation; 3) to produce a gene expression profile for AHR initiated cell death signaling in oocytes using a microscale gene array technology recently developed for small biological samples; 4) to delineate the role of nucleotide sequences flanking the "core" five-nucleotide AHRE in the bax gene promoter in specifying responses to the AHR activated by PAN versus dioxin; and, 5) to identify AHR-interacting proteins in oocytes, using matrix-assisted laser desorption and ionization/time-of-flight mass spectrometry (MALDI/TOF-MS), that may be involved in specifying cell lineage-selective induction of bax gene transcription by the PAN-activated AHR.

Publications:

Matikainen T, Perez GI, Jurisicova A, Pru JK, Schlezinger JJ, Ryu HY, Laine J, Sakai T, Korsmeyer SJ, Casper RF, Sherr DH, Tilly JL. Aromatic hydrocarbon receptor-driven Bax gene expression is required for remature ovarian failure caused by biohazardous environmental chemicals. Nature Genet. 2001 Aug;28(4):355-60.

Tilly JL, Kolesnick RN. Sphingolipids, apoptosis, cancer treatments and the ovary: investigating a crime against female fertility. Biochim Biophys Acta. 2002 Dec 30;1585(2-3):135-8. Review.

Morita Y, Perez GI, Paris F, Miranda SR, Ehleiter D, Haimovitz-Friedman A, Fuks Z, Xie Z, Reed JC, Schuchman EH, Kolesnick RN, Tilly JL. Oocyte apoptosis is suppressed by disruption of the acid sphingomyelinase gene or by sphingosine-1-phosphate therapy. Nature Medicine. 2000 Oct;6(10):1109-14.

Takai Y, Canning J, Perez GI, Pru JK, Schlezinger JJ, Sherr DH, Kolesnick RN, Yuan J, Flavell RA, Korsmeyer SJ, Tilly JL. Bax, caspase-2, and caspase-3 are required for ovarian follicle loss caused by 4-vinylcyclohexene diepoxide exposure of female mice in vivo. Endocrinology. 2003 Jan;144(1):69-74.

R01ES09246 Hoyer, Patricia B. University of Arizona
Signaling Pathways in Chemical Induced Ovotoxicity

Abstract: Women are exposed daily in the workplace, as well as the environment (cigarette smoke, automobile exhaust) to chemicals that can damage small pre-antral (primordial) ovarian follicles. Damage to these follicles can result in early ovarian failure (menopause). Because menopause is associated with a variety of health disorders, this represents a plausible health risk. Dosing of mice and rats with the occupational chemical, 4-vinyl-cyclohexene diepoxide (VCD) destroys primordial follicles and early ovarian failure can be caused in rodents by repeated dosing. On-going mechanistic studies in rats have helped characterize VCD as a model chemical for the study of xenobiotic-induced destruction of primordial follicles. However, the exact mechanisms which initiate oocyte degeneration remain unknown. Thus, it is proposed here to expand the base of mechanistic information obtained with VCD to further identify those mechanisms. Because a variety of environmental chemicals are known to destroy primordial follicles, VCD-related information will prove applicable to chemicals that are sources of greater exposure in the environment. The hypothesis to be tested is that VCD causes destruction of primordial follicles by upregulation of pre- and post-transcriptional intracellular pathways and the extent of this destruction is modulated by introvarian xenobiotic metabolizing capabilities. The Specific Aims are to: (1) identify and characterize gene expression directly regulated by VCD dosing, (2) dissect signaling pathways involved in VCD-induced ovotoxicity (3) characterize the ability of ovarian compartments to bioactivate and detoxify VCH, VCME, and VCD. Specifically investigating the mechanism(s) by which VCD damages ovarian primordial follicles will provide a greater ability to predict potential risks for early menopause from exposures to ovotoxic environmental chemicals in women. This greater awareness will lead to an appreciation of the global impact of the environment on age of menopause in women.

Publications:

Mayer LP, Pearsall NA, Christian PJ, Devine PJ, Payne CM, McCuskey MK, Marion SL, Sipes IG, Hoyer PB. Long-term effects of ovarian follicular depletion in rats by 4-vinylcyclohexene diepoxide. Reprod Toxicol. 2002 Nov-Dec;16(6):775-81.

Hoyer PB, Devine PJ, Hu X, Thompson KE, Sipes IG. Ovarian toxicity of 4-vinylcyclohexene diepoxide: a mechanistic model. Toxicol Pathol. 2001 Jan-Feb;29(1):91-9. Review.

R01ES12238 Whitsel, Eric A. University of North Carolina at Chapel Hill
The Environmental Epidemiology of Arrythmogenesis in the Women's Health Initiative

Abstract: Air pollution and cardiovascular disease mortality are clearly linked, yet population-based studies of air pollution and arrhythmogenesis have not been conducted in women. Moreover, extant studies have not evaluated whether acute, pro-arrhythmic effects of exposure to ambient air pollutants are modified by three potentially important markers of the environmental, socioeconomic and clinical context within which such exposures ostensibly increase cardiovascular risk in women: chronic exposure status, neighborhood of residence, and disease-specific susceptibility factors for sudden death. We will investigate these issues in an ethnically diverse population of 68,133 post-menopausal women aged 59-70 years from the 40 clinical centers and their satellites participating in the baseline examination of the Women's Health Initiative clinical trial (WHI, 1993-1998). We will estimate exposure to criteria pollutants (PM10; NO2; SO2; CO; 03) in ambient air at geocoded participant addresses using validated, spatial models that rely on pollutant concentrations recorded at adjacent fixed-site monitors in

the U.S. Environmental Protection Agency Aerometric Information Retrieval System. Spatially interpolated exposures will take the form of average pollutant concentrations on the day of, and for the 1, 2 & 3 days and 1, 2 & 3 years preceding the baseline examination and year three follow-up. We will reliably evaluate autonomic function, atrioventricular conduction, ventricular depolarization, ventricular repolarization and ectopy from resting, standard 12-lead ECGs recorded at the WHI examinations. After removing seasonal variations and long-term trends, and in addition, adjusting for demographic and meteorological covariates, we will explore the putative association between air pollutants and ECG measures. Then we will determine whether the associations are modified by chronic exposure status, socioeconomic characteristics of geographic regions in which participants live, and clinical risk factors for sudden cardiac death using Bayesian, hierarchical models. Lastly, we will assess sensitivity of our findings to adjustment for exposure measurement error arising from spatial interpolation of personal exposures from ambient concentrations of air pollutants. Our ancillary study will thereby evaluate the biologically relevant proarrhythmic mechanisms and contextual features linking ambient air pollution to cardiovascular disease morbidity and mortality in a large, ethnically and geographically diverse group of postmenopausal women. In doing so, it will improve understanding of associations between airborne pollutants and cardiovascular disease mortality, facilitate assessment of current U.S. air quality standards, and yield insight into the relatively gradual decline of sudden cardiac death rates among U.S. women over the last decade.

Publications: None

NIEHS Menopause Related Research 2004

Grant Number	PI Name	Project Title
Menopause		
1Z01ES049026-08	COOPER, GLINDA	Menstrual Patterns, Menopause, and Women's Health
1Z01ES040012-05	GLADEN, BETH	Organochlorines and their human health effects
2R01ES009246-05A1	HOYER, PATRICIA	Signaling Pathways in Chemical Induced Ovotoxicity
1Z01ES049030-08	SANDLER, DALE	Health Effects Of Exposures In Agriculture
1Z01ES049013-10	BAIRD, DONNA	Uterine Leiomyomas
5R01ES007171-09	ESKENAZI, BRENDA	Female Reproductive Outcomes and TCDD Exposure in Seveso
5R01ES012238-02	WHITSEL, ERIC	The Environmental Epidemiology of Arrythmogenesis in WHI
1U01ES012800-010001	HASLAM, SANDRA	Environmental Effects on the Molecular Architecture
1R15ES012182-01	MAY, JEFFREY	Neonatal Endocrine Disruption and Ovarian Senescence
5K08ES010963-04	LUDERER, ULRIKE	GSH: Protecting Ovarian Follicles from Oxidant Injury
5R01ES008430-08	TILLY, JONATHAN L.	Mechanisms of Aryl-Hydrocarbon-Induced Ovotoxicity
1Z01ES100327-02	MURPHY, ELIZABETH	Mechanism Of Cardioprotection In Females
5R21ES012272-02	GORE, ANDREA	Neuroendocrine outcomes of prenatal PCB exposures
Aging Women		
5P30ES007033-109010	FAUSTMAN, ELAINE	Core--Reproductive and Developmental Toxicology
5R21ES012272-02	GORE, ANDREA	Neuroendocrine outcomes of prenatal PCB exposures
1R01ES012916-01	PETROFF, BRIAN	Aryl hydrocarbon receptor pathway and reproductive aging
1R21ES013061-01	FLAWS, JODI	Long-term Consequences of Fetal Endocrine Disruption
5R01ES012238-02	WHITSEL, ERIC	The Environmental Epidemiology of Arrythmogenesis in WHI
1Z01ES049013-10	BAIRD, DONNA	Uterine Leiomyomas
1Z01ES049026-08	COOPER, GLINDA	Menstrual Patterns, Menopause, and Women s Health
1R15ES012182-01	MAY, JEFFREY	Neonatal Endocrine Disruption and Ovarian Senescence
Hormone Therapy and Women		
5R01ES009418-07	SHIBUTANI, SHINYA	Genotoxicity of Estrogen-and Anti-estrogen-DNA Adducts
1Z01ES049013-10	BAIRD, DONNA	Uterine Leiomyomas
1Z01ES025034-10	ZELDIN, DARRYL	Characterization & Functional Significance Of P450s
1Z01ES070065-28	KORACH, KENNETH	Chemical Receptor Interactions In Reproduction And Hormo
1Z01ES100327-02	MURPHY, ELIZABETH	Mechanism Of Cardioprotection In Females

National Institute of General Medical Sciences

(NIGMS)

National Institute of General Medical Sciences
Menopause Related Research 2004

Title Menopause, Symptoms, Blood Pressure and Health Risk in Hawaii's Multiethnic Population
Principal Investigator: Daniel E. Brown, Ph.D.
Grant Number: S06-GM008073
Priority Score: 202
MPRC-B Workgroup 4

DESCRIPTION (provided by applicant): Women's risk of cardiovascular disease increases upon menopause. Hot flashes, a common symptom associated with menopause, lead to both discomfort and elevated blood pressure. There are population differences in the age at which menopause is reached and in the frequency with which symptoms associated with menopause are reported. The current study proposes to examine ethnic differences in the age at menopause and experience of hot flashes in Hawaii's multiethnic population. The project has three components: a mailed survey of a random sample of adult women in Hilo Hawaii (N=1500), which includes questions about demographics, health and menopausal experience: an ambulatory monitoring of blood pressure and skin conductance over a 24-hour period of in a subsample (N=200) of these women that will also include collections of a blood sample for lipid analysis; and a laboratory investigation of objective and subjective measures of hot flashes and their physiological concomitants in the subsample of women under conditions that often induce hot flashes. Two study hypotheses are that there are significant ethnic differences in the percentage of women who report experiencing hot flashes, and that the peri- and post-menopausal women who report experiencing hot flashes will have higher mean daily B and elevated sleeping BP relative to same-age women who do not, or rarely, experience hot flashes. The implication of the research is that differences in the experience of menopause and its symptoms in peri- and postmenopausal women may explain some of the ethnic variation in cardiovascular health risk.

National Institute of Mental Health

(NIMH)

National Institute of Mental Health
Menopause Related Research 2004

Neuroprotective effects of estrogen in brain
Estrogen receptor (ER) activation has been shown to protect neurons in a number of different studies. However, it is unclear what the roles of the different types of estrogen receptor (ER alpha and ER beta) are in neuroprotection. To address this question, the investigators examined the impact of selective ER agonists for either ER alpha or ER beta to prevent the death of hippocampal neurons exposed to a toxin. Results indicated that both receptor subtypes could be involved in estrogen neuroprotection. As ER beta is highly expressed in the brain and has little or no expression in the breast or uterus, discovery and design of ER beta selective molecules could provide a strategy for activating the beneficial effects of estrogen in the brain without activating untoward effects of estrogen in reproductive organs.

Zhao L, Wu TW, Brinton RD. Estrogen receptor subtypes alpha and beta contribute to neuroprotection and increased Bcl-2 expression in primary hippocampal neurons. *Brain Res*. 2004 Jun 4;1010(1-2):22-34.

Estrogen modifies neuronal structure through novel mechanisms.
Estrogen (E) treatment induces branching of neurons in the hippocampus (an area of the brain involved in memory formation) of the rat. Results of this study showed that estrogen treatment of mice caused an increase in neuronal spine processes and molecular markers of increased neuronal synaptic communication within a subset of neurons of the hippocampus. These structural changes were associated with improved performance on a spatial episodic memory task. Taken together, the results suggest a previously uncharacterized role for estrogen in altering neuronal communication that is associated with enhancement of hippocampal-dependent memory.

Li C, Brake WG, Romeo RD, Dunlop JC, Gordon M, Buzescu R, Magarinos AM, Allen
PB, Greengard P, Luine V, McEwen BS. Estrogen alters hippocampal dendritic spine shape and enhances synaptic protein immunoreactivity and spatial memory in female mice. *Proc Natl Acad Sci* U S A. 2004 Feb 17;101(7):2185-90.

Akama KT, McEwen BS. Estrogen stimulates postsynaptic density-95 rapid protein synthesis via the Akt/protein kinase B pathway. *J Neurosci*. 2003 Mar 15;23(6):2333-9.

Estrogen receptor beta selective SERMS have antidepressant action in preclinical test
This study examined the actions of selective estrogen receptor modulators (SERMs) with different affinities for the intracellular estrogen receptor (ER) alpha or beta isoforms in a rodent behavioral test used to screen for antidepressant activity. Data from these studies suggest that estrogenic antidepressive effects may involve actions at ERbeta.

Walf AA, Rhodes ME, Frye CA. Antidepressant effects of ERbeta-selective estrogen receptor modulators in the forced swim test. *Pharmacol Biochem Behav*. 2004 Jul;78(3):523-9.

Estrogen treatment increases serotonin 2A receptors in postmenopausal women
In animal models, estrogen has been shown to influence serotonin receptors. Modulation of serotonin may be one way that estrogen affects mood and cognition. In this study, investigators examined the effect of estrogen on brain serotonin 2A receptors through the use of positron emission tomography (PET) scans in postmenopausal women to see whether there was any correlation of receptor changes with cognition and mood. Serotonin receptor binding was significantly increased after estrogen replacement in prefrontal areas of the brain. Verbal fluency and Trail Making Test performance, but not mood, were significantly improved by estrogen without correlation with receptor changes.

Kugaya A, Epperson CN, Zoghbi S, van Dyck CH, Hou Y, Fujita M, Staley JK, Garg PK, Seibyl JP, Innis RB. Increase in prefrontal cortex serotonin 2A receptors following estrogen treatment in postmenopausal women. *Am J Psychiatry*.2003 Aug;160(8):1522-4.

Relationship between menopausal hormone status and depression
Mood and reproductive function were prospectively evaluated in asymptomatic premenopausal women to determine whether the onset of depression was temporally linked to the perimenopause. Women followed through the onset of menopause with both hormonal and mood measures showed an increased risk of depression during the 24 months

surrounding the final menses, indicating that the late perimenopause may be a time of increased susceptibility to develop depression in some women. In a separate study, researchers examining the role of ovarian function and mood during the perimenopause, found that when ovarian function increased (demonstrated by higher lower levels of FSH) that mood improved in women with perimenopausal depression.

A longitudinal evaluation of the relationship between reproductive status and mood in perimenopausal women. Schmidt PJ, Haq N, Rubinow DR. *Am J Psychiatry*. 2004 Dec;161(12):2238-44.

Concordant restoration of ovarian function and mood in perimenopausal depression. Daly RC, Danaceau MA, Rubinow DR, Schmidt PJ. *Am J Psychiatry*. 2003 Oct;160(10):1842-6

NIMH Menopause Related Research 2005

Full Grant Number	Division	PI Name	Project Title
1Z01MH002537-15	IRP	SCHMIDT, PETER J	PSYCHOBIOLOGY AND TREATMENT OF PERIMENOPAUSAL MOOD DISOR
1Z01MH002648-12	IRP	CHIUEH, CHUANG C	NEUROPROTECTIVE STRATEGIES AGAINST BRAIN DISORDERS CAUSE
1Z01MH002659-12	IRP	GOLD, PHILIP W	THE NEUROBIOLOGY OF MAJOR DEPRESSION
1Z01MH002765-08	IRP	RUBINOW, DAVID	REPRODUCTIVE ENDOCRINE RELATED MOOD DISORDERS
5K08MH00 jsp/datavie		ALTEMUS, MARGARET	ESTROGEN EFFECTS ON ANXIETY RELATED NEURAL SYSTEMS
5R01MH059689-06	DMDBA	BROMBERGER, JOYCE T	MENOPAUSAL TRANSITION, MENTAL HEALTH AND ETHNICITY
7R01MH059891-05	DNBBS	FOSTER, THOMAS C	ESTROGEN AND COGNITION OVER THE LIFESPAN
5R01MH059919-05	DNBBS	PARRY, BARBARA L	MENOPAUSAL DEPRESSION: CHRONOBIOLOGIC BASIS
5R01MH059970-07	DNBBS	SHORS, TRACEY J	STRESS AND MEMORY FORMATION ACROSS THE FEMALE LIFESPAN
5R01MH060858-04	DNBBS	LERANTH, CSABA	ESTROGENIC EFFECT ON HIPPOCAMPAL THETA RHYTHM AND MEMORY
5R01MH061817-03	DNBBS	HERNDON, JAMES G	SELECTIVE ESTROGEN MODULATORS AND COGNITION
5R01MH062677-04	DNBBS	BETHEA, CYNTHIA L	OVARIAN STEROID REGULATION OF SEROTONIN IN PRIMATES
5R01MH063089-03	DNBBS	FREEDMAN, ROBERT R	SLEEP DISTURBANCE IN MENOPAUSE
5R03MH063932-02	DNBBS	ECKEL, LISA A	MECHANISM OF ESTROGEN'S INHIBITORY EFFECTS ON FEEDING
5R03MH065460-02	DNBBS	FRICK, KARYN M	ESTROGENIC-CHOLINERGIC INTERACTIONS IN MEMORY MODULATION
5R01MH065990-02	DNBBS	COHEN, ROCHELLE S.	ESTROGEN AND CAM KINASE IV IN THE LIMBIC SYSTEM
5K23MH066978-02	DMDBA	JOFFE, HADINE	PHYSIOLOGY OF ESTROGEN'S MOOD EFFECT IN MENOPAUSAL WOMEN
1R01MH067602-01A1	DNBBS	MELTZER, CAROLYN C.	AGE/SEX EFFECTS ON THE CENTRAL SEROTONIN SYSTEM

1R01MH069732-01A1	DMDBA	HARLOW, BERNARD L	RISK FOR NEW ONSET OF DEPRESSION IN PERIMENOPAUSAL WOMEN
1R03MH069780-01	DNBBS	AKAMA, KEITH T	NON-GENOMIC ACTIONS OF ESTROGEN ON SYNAPSE FUNCTION.
1R21MH069810-01A1	DNBBS	CALDWELL, JACK D	CHARACTERIZATION OF CENTRAL ABP/SHBG RECEPTORS
1R21MH070003-01A1	DNBBS	ARNSTEN, AMY F.T.	ESTROGEN, STRESS AND DYSFUNCTION OF PREFRONTAL CORTEX
1F32MH070086-01A1	DNBBS	JASNOW, AARON M	NEUROENDOCRINE MECHANISMS OF EMOTIONAL BEHAVIOR
1F31MH071085-01A1	DNBBS	COFER SMITH, CAROLINE D	ESTROGEN MODULATES HIPPOCAMPAL MORPHOLOGY AND PLASTICITY

Grant: 1Z01MH002537-15
Program Director:
Principal Investigator: SCHMIDT, PETER J N/A
Title: PSYCHOBIOLOGY AND TREATMENT OF PERIMENOPAUSAL MOOD DISOR
Institution: N/A

The goal of this project has been to examine the central nervous system effects of changes in reproductive endocrine function occurring in the context of hypogonadism. Investigations have been primarily focused on the characterization of affective disorders occurring during the perimenopause and midlife, the identification of the role of gonadal steroids in these mood disorders, and the examination of the neuroregulatory consequences of the presence and absence of gonadal steroids in women and men. Finally, the information obtained by these protocols will help identify the predictive utility of endocrine measures in perimenopausal depression and help define the role of hormonal therapies in mood disorders occurring at midlife in men and women. Findings to date: 1) a significant improvement in measures of depression and libido after DHEA administration was seen in 46 men and women with midlife-related major and minor depression; 2) neither gender nor plasma hormone levels predicted the therapeutic response to DHEA administration in midlife-related depression; 3) neither short term (six week) nor long term (six months-one year) administration of DHEA significantly altered measures of bone metabolism or bone density; 4) seven of 13 depressed perimenopausal women have experienced a remission of their depression during participation in a double-blind placebo-controlled trial of estradiol, phytoestrogens, and SERMs; 5) the SERM raloxifene was associated with an increase in plasma estradiol levels and a remission of mood symptoms in three (of three) perimenopausal depressed women. In a study involving the induction of hypogonadism in men and women with GnRH agonists, we have observed the hypogonadal state to be associated with the following: 1) the development of clinically significant mood symptoms in approximately 10% of hypogonadal men despite the presence of hot flushes and loss of libido in 90-100% of these men; 2) baseline evaluations of sexual functioning but not plasma hormone levels predicted the degree to which

sexual function was decreased after induced hypogonadism in both men and women (higher baseline sexual functioning was associated with greater declines in libido during hypogonadism); 3); CSF measures of the neurosteroid androsterone but not testosterone correlate with sexual function in men during both hypogonadism and testosterone replacement; and 4) the elimination in women of both cognition activated regional cerebral blood flow (O15 3D PET scans) in the dorsolateral prefrontal cortex and the reciprocal functional connectivity between the left hippocampal formation and the contralateral dorsolateral prefrontal cortex compared to either estradiol or progesterone replacement. In collaboration with NICHD we have observed that women with Turner Syndrome (n = 100) have significantly higher scores on measures of shyness, depression and anxiety than asymptomatic controls (n = 35) but their scores do not differ from those in women with premature ovarian failure (POF) (n =100). Finally, women with POF report an increased frequency of past episodes of depression compared to community samples of women, and the majority of these depressive episodes occurred in the context of menstrual cycle irregularity preceding their final menstrual period and the diagnosis of POF.

Grant: 1Z01MH002648-12
Program Director:
Principal Investigator: CHIUEH, CHUANG C N/A
Title: NEUROPROTECTIVE STRATEGIES AGAINST BRAIN DISORDERS CAUSE
Institution: N/A

Thioredoxin (Trx) is a multifunctional anti-oxidative and anti-apoptotic redox protein. We recently demonstrated that Trx can be induced by preconditioning procedures and drugs such as l-deprenyl and 17beta-estradiol. For managing progressive neurodegeneration such as Alzheimer's dementia and Parkinson?s disease we proposed to investigate the novel signaling pathway of NOS1-cGMP-PKG for increasing cytoprotective genes and antiapoptotic genes. Recent clinical trials of hormone replacement therapy indicated that hormone therapy's risks out weighed their benefits. These recent clinical reports are at odds with most of the recent preclinical studies; most of basic studies infer that estrogen and 17beta-estradiol may produce beneficial actions in the brain. Significant side effects of stroke, cancer and blood clots have been previously documented in clinical trials of contraceptive pills containing estrogen and progestin; most young women are willing to take risks over unwanted pregnancies. Menopausal women suffering from severe estrogen withdrawal symptoms may also need to make this kind of difficult decision. We investigated elusive actions of estrogen in the brain, which are likely mediated by nuclear estrogen receptors ERalpha and ERbeta. We employed 17beta-estradiol for investigating whether estrogen protects against neurodegeneration in human cell models. Physiological concentrations of 17beta-estradiol activate nuclear estrogen receptors (ERbeta>ERalpha) and up-regulate cGMP-dependent Trx expression. Moreover, l-deprenyl activates the signaling pathway of NO-cGMP-PKG also confers significant neuroprotection possibly through the induction of the redox protein Trx. Our collaborative integrated research project on neuronal adaptation, gene expression, and redox proteomics supports a new hypothesis that induction of NOS1 gene may result in cyto-and neuro-protection via induction of both antioxidative and anti-apoptotic proteins. Human SH-SY5Y cells were sensitive to oxidative stress-induced apoptosis since they contain relatively low levels of Trx. When these neurotrophic cells were subjected to a non-lethal preconditioning stress (2-hour serum deprivation), their NOS1 and Trx were up-regulated, and the cells became more tolerant of

oxidative stress with significant neurite extension, indicating that NO may compensatorily protect cells from free radical-induced apoptosis and result in neurotrophic cells with synaptogensis. In the present study, the contribution of Trx to the preconditioning mechanism by which NO/GSNO exerts its neuroprotective effects (hormesis) was investigated. Our results revealed that in addition to estrogen, l-deprenyl GSNO inhibits apoptosis through its ability to activate guanylate cyclase, which in turn activates the cGMP-dependent protein kinase (PKG). The activated PKG is required to protect cells from lipid peroxidation and apoptosis, to inhibit caspase-9 and caspase-3 activation, and to elevate the levels of Trx peroxidase-1, Trx, and Bcl-2. The induction of survival proteins was down stream to the signaling pathway of phosphorylated MAPK/ERK1/2, and c-Myc. Moreover, elevation of Trx, Trx peroxidase-1 and MnSOD inhibited oxidative stress and free radical generation. Interestingly, exogenously administered Trx also increased the synthesis of Bcl-2 and MnSOD leading to inhibition of lipid peroxidation and apoptotic cell death. Preconditioning-induced hormesis is mediated by the elevation of NOS1, NO, and cGMP, plus the biosynthesis of the redox protein Trx and associated Bcl2, MnSOD and trophic factors. For achieving neuroprotection, multi faceted therapeutics derived from Trx may be more effective than using large doses of a single antioxidant.

Grant: 1Z01MH002659-12
Program Director:
Principal Investigator: GOLD, PHILIP W N/A
Title: THE NEUROBIOLOGY OF MAJOR DEPRESSION
Institution: N/A

There are virtually no incontrovertible data elucidating the pathophysiology of the premature mortality, coronary artery disease, or osteoporosis seen in major depression. This is, of course, first and foremost an issue of patient survival and quality of life. Compelling data regarding pathophysiolgical mechanisms will also help formally establish major depression as a systemic disease in the general medical community. This, in turn, will elicit the surveillance of the medical community for systemic abnormalities in depressed patients, and the institution of effective preventive interventions to mitigate these systemic abnormalities. Contributing to this task could help highlight the urgency of diagnosing and treating depression, reduce the stigma of depression, and make it imperative for insurance companies to treat depression like any other systemic disease. We have identified an emerging metabolic syndrome in young, lean remitted patients with major depression, as well as premature osteoporosis, and are well on the way to ascertaining dysregulations among important mediators that could lead to the premature death and to both systemic manifestations. We found that compared to 47 BMI matched controls, remitted, young, lean patients with a major depressive illness had insulin resistance, increased plasma insulin, glucose, and triglyceride levels, as well as other serious sequella of insulin resistance and hyperinsulinism. Insulin exerts many adverse effects that are adaptive during acute stress but maladaptive when sustained. Insulin stimulates the secretion of proinflammatory cytokines such as IL-6, procoagulant compounds such as factor VIII, antifibrinolytic compounds such as PAI-1, and activates the sympathetic nervous system. We have found increased around-the-clock plasma IL-6 levels, and increased morning levels of factor VIII and PAI-1 levels, and unequivocal indices of sympathetic activation (the latter in patients with melancholic depression). It is of interest that both IL-6 and NE promote osteoporosis and coronary artery disease. One of our corollary goals is to identify common pathophysiolgical features that are

involved in both premature osteoporosis and coronary artery disease. This work could also extend concepts of the metabolic syndrome as a syndrome that includes both the metabolic abnormalities cited above as well as pathologic bone loss. Our finding of continuous elevations of plasma IL-6 levels has several implications. IL-6 has pleotropic effects and itself causes insulin resistance, increased inflammation, increased clotting, and decreased fibrinolysis. IL-6 is implicated as a highly significant factor in both atherosclerosis, which has a strong inflammatory component, as well and osteoporosis. Plasma IL-6 levels in healthy individuals are the best predictor of subsequent coronary artery disease, exceeding C-reactive protein (CRP) in its predictive value. IL-6 levels also predict osteoporosis, and IL-6 is among the most potent inducer of bone resorption. In the post-menopausal period, one of the important mechanisms posited for this condition is the loss of estrogen-mediated suppression of IL-6 release. We also found that a group of unmediated depressed patients with melancholic depression had high, around-the-clock central and peripheral hypersecretion of NE, as well as of plasma epinephrine, and cortisol secretion. While depressed, they also had increased blood pressure and pulse rates; all were reversible by a centrally directed treatment, ECT. CSF NE, plasma NE, and plasma cortisol rose and fell together throughout the 24 hour period, and rose progressively during EEG-documented sleep, peaking in the early morning, the time of the highest incidence of sudden death and myocardial infarction. Plasma EPI levels were also very high at this point, as were plasma IL-6 levels in our former study. Central NE activatiion and peripheral hypersecretion of plasma NE, EPI, and cortisol are all cardiotoxic, and their rising and falling together throughout the 24 hour period could have a particularly adverse effects. In addition, patients with chronic heart failure complicated by depression have a doubling of morbidity and mortality. NE levels no higher than in our depressed patients were the best predictor of subsequent mortality and morbidity in chronic heart failure. This finding provides a mechanism for the deleterious effect of depression when superimposed upon another systemic disease. We first found that premenopausal women with major depression have a marked increase in the prevalence of osteopenia and osteoporosis. Compared to 3-4% of the general premenopausal population, we found a 20-25% of osteopenia or osteoporosis in our depressed patients. Extrapolating from our data, we estimate that over 400,000 premenopausal women with major depression have osteopenia or osteoporosis as a consequence of their depression. Unfortunately osteoporosis is a silent disease until a fracture occurs. It is, however, a highly treatable illness, highlighting the need for early detection. The incidence of osteopenia and osteoporosis in premenopausal women is alarmingly high, and a significant public health hazard. In summary, depression increases premature mortality, coronary artery disease, and osteoporosis. Our group conducting a program of clinical and translational research to ascertain the pathophysiology of these phenomena.

Grant:	1Z01MH002765-08	
Program Director:		
Principal Investigator:	RUBINOW, DAVID	N/A
Title:	REPRODUCTIVE ENDOCRINE RELATED MOOD DISORDERS--DIFFERENT	
Institution:	N/A	

Gonadal steroids are major neuroregulators and presumably underlie gender-related differences (sexual dimorphisms) in brain structure and function. We have studied reproductive endocrine-related mood disorders as well as developed endocrine models for these disorders in order to characterize the role of gonadal steroids in affective disturbance. Our major recent findings are as follows: 1) Extension and confirmation of our preliminary demonstration that continuous administration of combined estradiol and progesterone eliminates premenstrual syndrome in the context of ovarian suppressive therapy (i.e., it is the change in hormones that precipitates depression in this subgroup); 2) Evidence from our ovarian suppression protocol that women with a history of non-puerperal depression resemble women with premenstrual dysphoria (PMD) in that the introduction of reproductive steroids precipitates a depression; 3) Demonstration that the HPA axis [CRH-stimulated ACTH and exercise-stimulated cortisol] is upregulated in men compared with women under hypogonadal conditions, (thus contradicting assumptions that observed dimorphisms were consequent to activational effects of gonadal steroids); 4) Evidence that gonadal steriods have different regulatory effects on the HPA axis in men and women, with testosterone decreasing (men) and progesterone increasing (women) CRH-stimulated cortisol; 5) Women with PMS metabolize progesterone differently from control women, with the decrease in allopregnanolone levels during continuous progesterone administration associated with symptom development in women with PMS but not controls. These observations are of both theoretical and practical import. They more precisely define the physiologic trigger of PMS and help identify the physiological modulators of the HPA axis (which is disturbed in PMS). Additionally, the data with continuous hormone administration may not only inform our understanding of the relevant hormonal stimuli that precipitate PMS, but as well may suggest a new therapeutic strategy for the millions of women who suffer from this disorder.

Grant:	5K08MH001682-05	
Program Director:	DESMOND, NANCY L	
Principal Investigator:	ALTEMUS, MARGARET	MD
Title:	ESTROGEN EFFECTS ON ANXIETY RELATED NEURAL SYSTEMS	
Institution:	WEILL MEDICAL COLLEGE OF CORNELL UNIV	NEW YORK, NEW YORK

DESCRIPTION: (Adapted from the Investigator's Abstract) This Mentored Clinical Scientist Development Award, a program of research and career development, is proposed to establish a foundation for future independent research in behavioral neuroscience, with a focus on reproductive hormones and emotional regulation. The research component of the proposal is a series of studies investigating the hypothesis that estrogen restrains fear associated behaviors.

Clinical data indicates that reproductive hormones fluxes have profound effects on the course of anxiety disorders and depression, but the neurobiological determinants of these clinical observations are not well understood. The specific aims of the research plan are to: 1) study the effects of estrogen on a battery of behavioral tests of anxiety; 2) examine the effects of estrogen on glucocorticoid and stress induced enhancement of fear behaviors; 3) examine the effects of estrogen on extrahypothalamic CRH and glucocorticoid receptors, a neuroendocrine system known to modulate fear and anxiety and 4) define the anatomic sites of estrogen action on fear behaviors. Fear associated neural circuits involving the amygsala, bed nucleus of the stria terminalis, and medial prefrontal cortex will be studied using local administration of estrogen and estrogen antagonists. The training portion of this proposal consists of basic neuroscience coursework and seminars as well as hands-on instruction in behavioral analysis and functional neuroanatomic techniques. Studies of the effects of estrogen on anxiety related neural systems provides an opportunity for the investigator to expand her area of expertise from clinical neuroendocrinology and clinical psychiatry to behavioral neuroscience where the effects of hormones on brain function can be studied more directly. This field of investigation is likely to improve understanding and treatment of anxiety and affective disorders, both of which are widely prevalent, chronic public health problems.

Grant:	5R01MH059689-06	
Program Director:	OTEY, EMELINE M.	
Principal Investigator:	BROMBERGER, JOYCE T	PHD
Title:	MENOPAUSAL TRANSITION, MENTAL HEALTH AND ETHNICITY	
Institution:	UNIVERSITY OF PITTSBURGH AT PITTSBURGH	PITTSBURGH, PENNSYLVANIA

DESCRIPTION (provided by applicant): This competing renewal application is a revision of what was previously a Collaborative R0l three site prospective study of middle-aged women's mental health that is an ancillary study of the Study of Women' Health Across the Nation (SWAN). Due to difficulty with retention and feasibility issues at the other 2 sites they will be unable to continue the study. We are proposing to continue the study in Pittsburgh only. 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. Our 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 (MOD) is risk factor for the following during the transition: (a) syndromal or subsyndromal depression, (b) increased levels of perceived stress, somatic and psychological symptoms, or (c) 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 a unique opportunity to expand knowledge of women's mental health in midlife and beyond.

Grant:	7R01MH059891-05	
Program Director:	ANDERSON, KATHLEEN C.	
Principal Investigator:	FOSTER, THOMAS C	PHD
Title:	ESTROGEN AND COGNITION OVER THE LIFESPAN	
Institution:	UNIVERSITY OF FLORIDA	GAINESVILLE, FLORIDA

The long-term goals of this research are to understand the mechanisms for the decline in hippocampal-dependent memory function during aging. The incidence of Alzheimer s disease is projected to nearly quadruple in the next 50 years with the greatest prevalence in women. Importantly, estrogen treatment can delaying the progression of memory loss associated with aging and Alzheimer s disease. However, little is known concerning which of the many estrogen associated effects on brain function are important for memory. The discovery of several different estrogen receptors (Ers) within the hippocampus makes this challenge more formidable. Recent studies suggest that age- related memory impairment is due to changes in the threshold for synaptic modification thought to underlie memory storage processes. In turn, threshold changes are linked to altered Ca2+ homeostasis during aging. Interestingly, the influence of estradiol (E2) on Ca2+ homeostasis is diametrically opposed to the changes observed in aged memory impaired animals. The proposed studies test the hypothesis that E2 effects on memory are due to changes in the susceptibility to synaptic modification as a result of altered Ca2+ homeostasis processes. The proposal has three specific aims. First we will characterize the effects of E2 replacement, at physiologically relevant doses, on tasks that are sensitive to hippocampal-dependent memory function. In addition, these studies will employ female Eralpha knockout mice to determine whether Eralpha activation is involved in E2 mediated effects on memory. Second, we will test the hypothesis that E2 effects on memory are mediated by changes in the thresholds for synaptic plasticity. It is predicted that the frequency-response function for synaptic plasticity is transformed by E2 replacement due to a shift in the threshold for synaptic modification, and memory function will correlate with synaptic plasticity. Thirdly, we will test the hypothesis that E2 mediated changes in synaptic modification are due to nongenomic mechanisms that rapidly regulate Ca2+ homeostasis and cell excitability. For these studies, the effect of E2 on the Ca2+-dependent processes including synaptic plasticity will be examined in the hippocampal slice. We believe that the results of our experiments will add significantly to our knowledge concerning the regulation of synaptic function across the life span and provide a basis for understanding the mechanism for estrogen s effects of memory.

Grant:	5R01MH059919-05	
Program Director:	BRADY, LINDA S.	
Principal Investigator:	PARRY, BARBARA L	MD
Title:	MENOPAUSAL DEPRESSION: CHRONOBIOLOGIC BASIS	
Institution:	UNIVERSITY OF CALIFORNIA SAN DIEGO	LA JOLLA, CALIFORNIA

No Abstract Available

Grant:	5R01MH059970-07	
Program Director:	LEDERHENDLER, ISRAEL I	
Principal Investigator:	SHORS, TRACEY J	PHD
Title:	STRESS AND MEMORY FORMATION ACROSS THE FEMALE LIFESPAN	
Institution:	RUTGERS THE ST UNIV OF NJ NEW BRUNSWICK	NEW BRUNSWICK, NEW JERSEY

DESCRIPTION (provided by applicant): It has become increasingly clear that males and females differ even more dramatically than we previously thought. Not only do they exhibit differing responses to stress and environmental experience, but they can also respond in opposite directions. In rats, exposure to an acute stressful event enhances associative learning in males while dramatically impairing performance in females (Wood et al 2001, Wood & Shors 1998; Shors et al., 1998, 2002). These opposite effects of stress on memory formation are accompanied by similarly opposite effects on the presence of dendritic spines in the hippocampal formation (Shors et al 2001). Moreover, these opposite effects of stress are mediated by different hormonal systems between the sexes (Wood et al 2001, Beylin & Shors 2002). Sex differences usually arise from activational and organizational effects of sex hormones which fluctuate across the lifespan, especially in females. The experiments described in this competing continuation capitalize on hormonal fluctuations and changes in emotionality that occur during very early development, puberty, post-partum and menopause. They are designed to associate and dissociate changes in learning ability and responses to stressful experience with changes in hormones and density of dendritic spines in the hippocampal formation. Finally, experiments are designed to explore a potential relationship between sex differences in learning and the expression of growth hormone (GH) in the hippocampus, a gene that is preferentially induced by learning (Donahue et al., 2002). Techniques include trace eyeblink conditioning in the rat, Golgi impregnation and light microscope analysis, real-time polymerase chain reaction, in situ hybridization, radioimmunoassay, and surgical manipulation of glucocorticoids and ovarian hormones. Overall, these studies will identity the neuronal and hormonal mechanisms that underlie sex differences in learning and opposite responses to stressful experience in males versus females. Because mental disorders often emerge or are exacerbated during these life changes, the studies will provide insight into sex differences in mental illness, especially those experienced so frequently by women: post-traumatic stress disorder (PTSD), unipolar, post-partum and post-menopausal depression, as well as Alzheimer's disease.

Grant:	5R01MH060858-04	
Program Director:	ANDERSON, KATHLEEN C.	
Principal Investigator:	LERANTH, CSABA	MD
Title:	ESTROGENIC EFFECT ON HIPPOCAMPAL THETA RHYTHM AND MEMORY	
Institution:	YALE UNIVERSITY	NEW HAVEN, CONNECTICUT

DESCRIPTION: (Adapted from applicant's abstract): Recent evidence indicates that estrogen treatment in ovariectomized rats enhances performance on memory tasks. Similarly, human observations suggest a beneficial effect of estrogen treatment on cognitive function in Alzheimer's disease. However, those cellular targets of gonadal hormones that are directly involved in memory processes are ill defined. The only solid observations are that systemic hormonal manipulations result in changes in the density of spines and alterations in the intensity of immunostaining for NMDA receptor of hippocampal CAl pyramidal cells. However, hippocampal principal neurons themselves do not, only a small population of interneurons contains nuclear estrogen receptor. On the other hand, neurons in subcortical areas, including the medial septum diagonal band of Broca (MSDB), supramammillary area (SUM), and median raphe (MR) contain nuclear estrogen receptors, and these structures are associated with the generation/regulation of hippocampal theta activity and long term potentiation. Furthermore, hippocampal theta activity, which is greatly influenced by the changing levels of circulating estrogen, in conjunction with long-term potentiation is believed to be involved in memory processes. Therefore, the hypothesis that estrogen, in addition to influencing the hippocampus directly, regulates mnemonic processes by affecting these subcortical areas will be tested by experiments designed to examine the effects of intra-MR, -MSDB, and -SUM administration of estrogen in ovariectomized rats on: 1) changes in dendritic spine density of hippocampal CAl pyramidal cells; 2) mRNA and peptide levels of ionotropic glutamate receptors in the hippocampus; 3) hippocampal theta activity.

Grant:	5R01MH061817-03	
Program Director:	WINSKY, LOIS M.	
Principal Investigator:	HERNDON, JAMES G	PHD
Title:	SELECTIVE ESTROGEN MODULATORS AND COGNITION	
Institution:	EMORY UNIVERSITY	ATLANTA, GEORGIA

Estradiuol (E2) replacement therapy (ERT) in menopausal women has protective effects on a variety of age-related diseases, including osteoporosis, cardiovascular diseases, age-related memory impairments, and development of dementia. However, ERT, even with progestin co-treatment, induces precancerous changes in the tissues of the breast and uterus. A new group of non-steroidal estrogens, deemed Selective Estrogen Receptor Modulators (SERMs) has been developed as a possible alternative to ERT but without the adverse proliferative effects on breast and endometrial tissues, while retaining some of the positive effects of E2. Yet, despite the well-documented efficacy of these compounds in peripheral target tissues, their influence in the brain, and especially upon cognitive function, is not known. Clearly brain and cognitive effects of SERMs must be understood in order to determine their desirability as an alternative to ERT in hypoestrogenic women. We will use the ovariectomized rhesus monkey as a model of human low-estrogen conditions, such as menopause, to examine the effects of SERMs on female cognition. This project will first determine whether the SERMs tamoxifen and raloxifene are E2 agonists or E2 antagonists in a variety of cognitive domains in Ovariectomized female rhesus monkeys. Monkeys will be repeatedly tested with a computerized touch- screen system on a battery of four memory and attentional tasks while undergoing E2, SERMs, or placebo treatments. Specific Aim 2ill use the same battery of tasks to determine whether SERMs, in the presence of E2, act as E2 antagonists on cognitive function. Specific Aim 3 will use positron emission tomography (PET) and the glucose metabolic tracer [18F]fluorodeoxyglucose (18F

FDG) to determine whether E2 increases activation of specific brain regions following performance on the cognitive task most improved by ERT. Specific Aim 1 will determine whether SERMs mimic E2 in enhancing object recognition memory, attention, and working memory, while impairing spatial memory functions in ovariectomized female rhesus monkeys. Specific Aim 2 will determine whether SERMs, in the presence of E2, act a sE2 antagonists in cognitive function/ Specific Aim 3 will use PET and the 18F FDG tracer to evaluate the relationships between rCMRglc, ERT, and cognitive performance on a specific task. These data in the rhesus monkey will provide valuable information on the efficacy of SERMs on female cognition and will help in evaluating the risks and benefits of using these compounds in hypoestrogenic women.

Grant:	5R01MH062677-04	
Program Director:	WINSKY, LOIS M.	
Principal Investigator:	BETHEA, CYNTHIA L	PHD
Title:	OVARIAN STEROID REGULATION OF SEROTONIN IN PRIMATES	
Institution:	OREGON HEALTH & SCIENCE UNIVERSITY	PORTLAND, OREGON

DESCRIPTION (applicant's abstract): The previous interest of this laboratory in the neural regulation of progestin-induced prolactin secretion in primates has evolved into a broader interest in the regulation of serotonin neural function by ovarian steroids. The serotonin neural system projects to nearly every area of the forebrain and serotonin plays a major role in the regulation of numerous autonomic and cognitive neural processes. Thus, understanding the action of ovarian steroids in the serotonin neural system has relevance to many aspects of mental health and function in women. This proposal continues our search, at a cellular and molecular level, for neural targets of progesterone (P) which are unique from the action of estrogen (E) and it initiates studies to determine the mechanism by which E exerts differential effects on the expression of 3 pivotal genes: tryptophan hydroxylase (TPH), the serotonin reuptake transporter (SERT), and the 5-HT1A autoreceptor, in serotonin neurons of macaques. The overall hypothesis is that progesterone (P) has unique, undiscovered, genomic actions in the serotonin neural system which elevate 5-HT neurotransmission. Estrogen (E) is required for the induction and maintenance of nuclear P receptors and E alone changes the expression of pivotal genes related to serotonin synthesis, uptake, and neuronal firing. The molecular actions of E may be mediated by ER-beta and could involve a protein-protein interaction with nuclear factor kappa B (NF-kB). Aim 1 will obtain definitive evidence that addition of P to an E regimen increases serotonin neurotransmission by application of microdialysis and measurement of serotonin in the extracellular compartment of terminal fields in steroid-treated macaques. Aim 2 will determine the functional consequences of previously reported changes in TPH, SERT, and 5-HT1A autoreceptor gene expression in serotonin neurons of macaques treated with E and P. Aim 3 will determine the effect of E and P on degradative mechanisms of serotonin. Gene expression and function of monoamine oxidase (MAO-A) will be determined in the dorsal raphe and hypothalamic termina1 field. Aim 4 will seek the expression of ER-beta and determine if nuclear factor kappa B (NF-kB) is co-expressed and regulated by E or P in serotonin neurons of macaques. Aim 5 will use laser capture to obtain pure populations of serotonin neurons from steroid-treated macaques and amplify their RNA for examination of genes related to phosphorylation events. These experiments will (1) further the hypothesis that E and P increase

serotonin neural function and (2) initiate investigations of the mechanism of action of E and P in serotonin neurons.

Grant:	5R01MH063089-03	
Program Director:	BABCOCK, DEBRA J.	
Principal Investigator:	FREEDMAN, ROBERT R	PHD
Title:	SLEEP DISTURBANCE IN MENOPAUSE	
Institution:	WAYNE STATE UNIVERSITY	DETROIT, MICHIGAN

At present, over 35% of the women in the United States have reached the median age of menopause, 51 years. Hot flashes (HFs) are the most common symptom of the climacteric and occur in the vast majority of postmenopausal women. Sleep disturbance has also been reported to be highly prevalent in this population. Yet, the causal links, if any, between these 2 phenomena are I not known. In the studies proposed here, we will attempt to discern the relationships among Hfs and objective and subjective sleep disturbance. In Study 1, we will record sleep and HF parameters in postmenopausal women with HFs, those without HFs, and age-matched premenopausal women without HFs. We will perform quantitative EEG analyses, use an objective test of daytime sleepiness (MSLT) and assess subjective sleep quality with established instruments. HF frequency increases with ambient temperature. If HFs produce arousals and thereby disrupt sleep, then reducing ambient temperature should improve sleep and increasing temperature should worsen it (Study 2). Increased arousal frequency has been found in postmenopausal women with HFs. If this accounts for reports of poor sleep, then experimental sleep disruption in asymptomatic women should produce reports of poor sleep, as well. In Study 3, we will use yoked groups of symptomatic and asymptomatic women and disrupt sleep of the latter group based on recordings from the former group. We will do this using a stimulus specific to HFs (ambient heating). Despite the common use of hormone replacement therapy, its effects on sleep have not been established. In Study 4, we will systematically manipulate ambient temperature during sleep in symptomatic women before and during estrogen replacement and in a placebo-control group. In Study 5, we will determine the effects of elevated sympathetic activation on HFs and sleep using a stimulus that does not, by itself, disrupt sleep (orthostasis).

Grant:	5R03MH063932-02	
Program Director:	WINSKY, LOIS M.	
Principal Investigator:	ECKEL, LISA A	PHD
Title:	MECHANISM OF ESTROGEN'S INHIBITORY EFFECTS ON FEEDING	
Institution:	FLORIDA STATE UNIVERSITY	TALLAHASSEE, FLORIDA

DESCRIPTION (provided by applicant): The ovarian cycle has profound effects on food intake in a variety of species, including humans. This effect is very prominent in female rats which display a 20 - 40 percent decrease in food intake during the estrous (sexually receptive) phase of the cycle. This decline in food intake during estrus appears to be mediated, at least in part, by increased sensitivity to the satiety effects of cholecystokinin (CCK), a gut peptide that is released during meals and functions to decrease food intake by generating a satiety signal that is relayed

to the brain via the vagus nerve. The importance of the rat's ovarian cycle in the control of food intake is revealed by ovariectomy, which increases food intake, decreases sensitivity to CCK, promotes body weight gain and, in the absence of estrogen replacement, induces obesity. Although the decline in estrogen activity appears to mediate the hyperphagia and associated body weight gain following ovariectomy, it is not known whether changes in endogenous estrogen activity mediate the decrease in food intake and increase in CCK satiation expressed during estrus in cycling rats. One goal of this proposal is to determine whether antagonism of central estrogen receptor activity will block the estrous-related decrease in food intake and increase in CCK satiation. To investigate this hypothesis, food intake and meal patterns will be monitored in cycling rats treated with an antiestrogen at various phases of the estrous cycle. A second goal is to use c-Fos immunocytochemistry, a marker of neuronal activity, to determine whether increased sensitivity to the satiety effects of CCK during estrus is mediated by increased responsivity of neurons that process satiety signals generated by consumption of a meal and by injection of CCK. A third goal of this proposal is to determine the brain areas where endogenous estrogen acts to decrease food intake and increase CCK satiation during estrus. In this experiment, in situ hybridization and immunocytochemistry techniques will be combined to determine whether those neurons that are activated by CCK express estrogen receptors. Together, these studies have the potential to broaden our understanding of the mechanism by which food intake is controlled across the estrous cycle of female rats. Because eating disorders are more prevalent in women than in men, this proposal targets an important research question with clear clinical relevance .

Grant:	5R03MH065460-02	
Program Director:	ANDERSON, KATHLEEN C.	
Principal Investigator:	FRICK, KARYN M	PHD
Title:	ESTROGENIC-CHOLINERGIC INTERACTIONS IN MEMORY MODULATION	
Institution:	YALE UNIVERSITY	NEW HAVEN, CONNECTICUT
Project Period:	2002/12/01 - 2004/11/30	

No Abstract Available

Grant:	5R01MH065990-02	
Program Director:	WINSKY, LOIS M.	
Principal Investigator:	COHEN, ROCHELLE S.	PHD
Title:	ESTROGEN AND CAM KINASE IV IN THE LIMBIC SYSTEM	
Institution:	UNIVERSITY OF ILLINOIS AT CHICAGO	CHICAGO, ILLINOIS
Project Period:	2003/09/30 - 2007/08/31	

DESCRIPTION (provided by applicant): Clinical studies have shown that estrogen (E2) can ameliorate symptoms of mood disorders in women, including severe depression. The presence of

symptoms may represent an abnormal response to normal hormonal changes, thereby implicating contextual factors in the brain in the etiology of these symptoms. Some of these factors include second messenger systems that lead to the production of neurotrophic agents, including brain-derived neurotrophic factor (BDNF). Chronic stress results in deleterious effects on neurons and synapses which, in turn, may be related to alterations in affective behavior. Because of its involvement in cellular and synaptic growth and/or function, BDNF may counteract these negative effects and restore the appropriate behavioral responses. The gene transcription factor cyclic AMP response element-binding protein (CREB), has been shown to be a target of antidepressant and E2 action. Activation of CREB can lead to transcription of the BDNF gene. We propose that the Ca2+/calmodulin-dependent protein kinase IV (CaMK IV) pathway, "CaMK IV - CREB - phosphorylated CREB (pCREB) - BDNF," mediates some of the effects of long-term E2 treatment on behavior. Long-term E2 treatment results in the persistence of these messengers, even after two weeks. E2 may regulate CaMK IV and BDNF via alterations in their mRNAs; we will perform in situ hybridization to address the hypothesis that E2 regulates levels of CaMK IV mRNA and BDNF mRNA. We will also determine if E2 decreases relevant phosphatases, including protein phosphatase 2A and the calcineurin pathway, negative regulators of CaMK IV and pCREB, respectively. To determine if CaMK IV, CREB and/or BDNF mediate E2 effects in the forced swim test, a test for the efficacy of antidepressants in rodents, antisense oligodeoxynucleotides (ODNs) to CaMK IV, CREB or BDNF will be infused into the amygdala or hippocampus and animals will be subjected to the test conditions. Infusion of these antisense ODNs may interfere with the positive effects of E2 on forced swim. We will also determine if infusions of BDNF protein with the antisense ODNs to CaMK IV and CREB reverse the actions of the ODNs on behavior. These experiments will give insight to the molecular effects of E2 in areas of the brain related to affective processing and will uncover mechanisms that may allow hormonal intervention for the amelioration of female-related mood disorders.

Grant:	5K23MH066978-02	
Program Director:	DOLAN-SEWELL, REGINA	
Principal Investigator:	JOFFE, HADINE	MD
Title:	PHYSIOLOGY OF ESTROGEN'S MOOD EFFECT IN MENOPAUSAL WOMEN	
Institution:	MASSACHUSETTS GENERAL HOSPITAL	BOSTON, MASSACHUSETTS

DESCRIPTION (provided by applicant): This Mentored Patient-Oriented Career Development Award focuses on developing expertise in the interdisciplinary field of perimenopausal depression. Menopause is universal in women, and depressive disorders occur in 10% of perimenopausal women. This project will dissect the mechanisms by which estrogen replacement therapy (ERT) treats depression in menopausal women. We hypothesize that ERT improves mood by a direct CNS effect, rather than by simply treating hot flushes and sleep disruption. A physiologic intervention study will compare the mood effect of ERT with that of a hypnotic agent in depressed perimenopausal women. The direct neuromodulatory effect of ERT on mood will be unmasked by controlling for ERT's effect on sleep. Polysomnographic (PSG) studies will be used to explore changes in sleep architecture that occur with ERT and the hypnotic agent zolpidem. This study will: (1) identify the elements critical to estrogen's antidepressant benefit; (2) characterize subpopulations of perimenopausal women whose depression can be treated with

non-hormonal therapies and those who require treatment with ERT; and (3) define optimal management of depression in perimenopausal women. Understanding the components of ERT's effect on mood will also advance the field of hot-flush research by examining the impact of hot flushes on sleep, mood, and quality-of-life. This is critical for the development of novel estrogen alternatives and putative hot-flush therapies increasingly used in women with breast cancer and others unable or unwilling to take ERT. ENVIRONMENT: The proposed study will be based at Massachusetts General Hospital (MGH), with outstanding interdisciplinary sponsorship and consultant input. PSG studies will be performed at McLean Hospital. I will receive mentorship from Lee Cohen, M.D., in the Department of Psychiatry, and Janet Hall, M.D., in the Reproductive Endocrinology Unit of the Department of Medicine at MGH. Both sponsors are internationally recognized in their respective fields and have exceptional track records as effective research mentors. Their combined expertise will shape my career development in this interdisciplinary field. CAREER DEVELOPMENT PLAN: Physiologic investigation of mood disturbance in menopausal women requires that I acquire knowledge of (1) sleep medicine; and (2) research methods for healthoutcomes assessment and clinical intervention studies using physiologic measures. I will receive formal training in each of these specific research areas under the supervision of expert consultants. Such training will lay the foundation for a career of clinical investigation into the physiology of perimenopausal depression and the impact of hot flushes on sleep, mood, and quality-of-life.

Grant:	1R01MH067602-01A1	
Program Director:	BRADY, LINDA S.	
Principal Investigator:	MELTZER, CAROLYN C.	MD
Title:	AGE/SEX EFFECTS ON THE CENTRAL SEROTONIN SYSTEM	
Institution:	UNIVERSITY OF PITTSBURGH AT PITTSBURGH	PITTSBURGH, PENNSYLVANIA

DESCRIPTION (provided by applicant): Advances in molecular biology and neuroimaging, coupled with the imperative caused by the aging of the population, have created fertile ground for improved understanding of the interaction between brain function and behavior. It is well recognized that the integrity of the central serotonin (5-HT) neurotransmitter system is essential for the proper regulation of mood, behavior, and memory. Selective age effects on the 5-HT system may impact risk and manifestations of depression across the lifespan and cognitive impairment in the elderly. Further, mood disorders and Alzheimer's disease affect a disproportionate number of women, yet the etiology and potential treatment implications of this gender association are understudied. Indeed, sex differences in the effect of age on the 5-HT system is of etiologic and therapeutic importance to potential gender influences on susceptibility, course, and treatment of mood and cognitive disturbances in normal aging and in association with neurodegenerative disease. The aim of this proposal is to define the role of aging and the potential influence of gender on serotonergic function. This study focuses on two complementary 5-HT receptor subtypes, 5-HT1A and 5-HT2A, because of their association with depression and memory function and putative role in mechanisms of antidepressant treatment response; further, these receptor subtypes are pharmacologically well-characterized and amenable to in vivo study in humans with new highly selective ligands for positron emission tomography (PET). Quantitative image analysis will include a magnetic resonance (MR) imaging-based partial

volume correction developed by the PI in order to minimize the diluting effects of cerebral atrophy, a source of bias that frequently confounds PET studies of aging. The goal of this work is to provide unique and direct information on the effect of age and potential influence of sex on human serotonergic function. Thus, this revised R01 application complements our funded R01 (MH59945), which uses PET and serotonergic ligands to investigate treatment response mechanisms in late-life depression. The current proposal further reinforces the strong commitment by the PI and colleagues to apply advanced quantitative in vivo imaging techniques to define neurobiologic correlates of aging and neuropsychiatric disorders of late life.

Grant:	1R01MH069732-01A1	
Program Director:	COLPE, LISA J.	
Principal Investigator:	HARLOW, BERNARD L	PHD
Title:	RISK FOR NEW ONSET OF DEPRESSION IN PERIMENOPAUSAL WOMEN	
Institution:	BRIGHAM AND WOMEN'S HOSPITAL	BOSTON, MASSACHUSETTS

DESCRIPTION (provided by applicant): Several epidemiological studies have shown that women, compared to men, are at a substantially greater risk of depression beginning in adolescence and continuing through their entire life. In addition, the age-specific incidence of depression in women peaks during the late reproductive years. However, the extent to which the perimenopause represents a time of greater risk for new onset of depression in women with no history of mood disorder is yet to be determined. The Harvard Study of Moods and Cycles (HSMC), a population-based prospective study of late premenopausal aged women, is uniquely suited to investigate this association because of the rigorous systematic assessment of psychiatric morbidity and menstrual cycle changes over time. In this study, approximately 1000 premenopausal women with and without a lifetime history of depression were followed over 36 months with semi-annual psychiatric assessments, medical history interviews, and early follicular phase blood specimens to measure reproductive hormones in serum. Our published results have shown that 1) age at menarche and other events in early reproductive life are associated with risk for depression, 2) women with a lifetime history of major depression (particularly those with more severe depressive symptoms proximate to the perimenopause) are at a greater risk of developing menstrual cycle changes consistent with those that signal an earlier transition to the perimenopause compared to women with no depression history, and 3) early follicular phase FSH and LH are higher, and estradiol levels are lower in depressed compared to non-depressed late reproductive aged women as they move toward the climacteric. Having carefully gathered prospective data on psychiatric disorders and changes in menstruation, we now have a unique opportunity to evaluate the impact of the perimenopausal transition on risk of first onset of mood disturbance. In this current submission, we plan to include approximately 500 women from the original HSMC with no lifetime history of major depression, and will enrich this sample with an additional 200 largely minority women from the general population. Our preliminary data suggest that an earlier onset to the perimenopausal transition is associated with a 3-fold risk of new onset of major depression in women with no prior history of depressive disorder. Furthermore, it appears that initiation of hormonal therapy to treat menstrual cycle changes, irregularities, or somatic symptoms attenuates this increased risk of a first onset of depressive episode. We plan to better assess the effect of onset to the perimenopause on the

risk for new onset of mood disturbance independent of past depression history that clearly influences the risk of recurrent episodes. The present project is designed to confirm and expand upon these preliminary findings by using structured clinical interviews for accurate psychiatric diagnoses, and comprehensive assessments of clinical symptoms at the time of the menopausal transition.

Grant:	1R03MH069780-01	
Program Director:	WINSKY, LOIS M.	
Principal Investigator:	AKAMA, KEITH T	PHD
Title:	NON-GENOMIC ACTIONS OF ESTROGEN ON SYNAPSE FUNCTION.	
Institution:	ROCKEFELLER UNIVERSITY	NEW YORK, NEW YORK

DESCRIPTION (provided by applicant): In aging, decreased levels of circulating estrogen are associated with memory impairment and cognitive decline, but the molecular events underlying this dysfunction are poorly understood. Therefore, the broad, long-term goal is to understand how estrogen supports synaptic activity, with particular focus on the hippocampus, the area of the brain associated with learning and memory. The specific goal of this project is to define the molecular pathways by which estroqen regulates NR1, the obligate subunit of the NmethyI- D-aspartate (NMDA) receptor (NMDAR). Mice lacking NR1 display an absence of hippocampal synaptic plasticity and have impaired spatial memory. In wild-type animals, endogenous increases in estrogen across the estrous cycle are associated with improved spatial memory, increased NR1 protein levels, and increased NMDAR binding in the hippocampus. Preliminary data indicate that estrogen also can directly increase NR1 mRNA levels in vitro, yet there are no estrogen receptor (ER) response elements in the genomic NR1 promoter. Therefore, the testable hypothesis is that estrogen stimulates NR1 activity and thus supports consequent synaptic function -- using non-genomic mechanisms on both promoter activation as well as post translational modification. The project has four independent yet inter-related aims: Aim 1 will quantify estrogen-stimulated increases in NR1 mRNA levels by using organotypic hippocampal slice cultures and quantitative RT-PCR to achieve significant sensitivity over current in vivo approaches. Aim 2 will quantify the non-genomic actions of estrogen on the NR1 promoter using NR1 reporter constructs and mutant variants. Aim 3 will determine how different ER isoforms (ERalpha or ERbeta) lead to NR1 promoter modulation. Aim 4 will determine how non-genomic estrogen actions post-translationally phosphorylate NR1 to modify NMDAR localization, sensitivity, and activity at the synapse. The NMDAR is the major glutamatergic receptor in the hippocampus, and deficit in NR1 is associated with aging and human neurologic diseases. This project will elucidate how estrogen nongenomically stimulates and supports cognitive function by promoting synaptic activity in hippocampal neurons, and, by corollary, will explain one way the loss of estrogen may affect neuronal dysfunction observed in the aging process.

Grant:	1R21MH069810-01A1	
Program Director:	WINSKY, LOIS M.	
Principal Investigator:	CALDWELL, JACK D	MD
Title:	CHARACTERIZATION OF CENTRAL ABP/SHBG RECEPTORS	

Institution:	UNIVERSITY OF ILLINOIS AT CHICAGO	CHICAGO, ILLINOIS

DESCRIPTION (provided by applicant): An emerging model of action for steroid-binding proteins is that they are essential in delivering steroids to either steroid membrane or cytoplasmic receptors. Whereas the more commonly known model suggests that steroid-binding proteins such as sex hormone binding globulin (SHBG) are only made in the periphery and only deliver steroids to be passively released at the target cell, we have found that SHBG is produced in the brain where it facilitates female sexual receptivity. Therefore, we have two ends of the answer to the question of whether SHBG is a neuromodulator: its production and its behavioral effects. However, we need to find out whether and where there are receptors for SHBG in brain. In generating preliminary data, we have found that SHBG stimulates female sexual receptivity and that coupling it to dihydrotestosterone blocks this facilitative effect. We have found that microiontophoresing SHBG onto hypothalamic tissue sections results in an immediate depolarization of magnocellular neurons. We have found that cells transfected with either estradiol receptor alpha or beta respond to both SHBG and SHBG-estradiol application with an elevation of MAP kinase phosphorylation. Using SELDI-TOF mass spectrometry on affinity chromatography eluted hypothalamic tissue, we have identified protein peaks at 144000 and 168000 daltons that seem to represent SHBG receptors. We have found SHBG produced in hypothalamic areas in the same neurons as the reproductively important peptide oxytocin. Both SHBG and oxytocin are found in varicosities and in synaptic vesicles suggesting they are released within the brain. Therefore, work done in several laboratories, collaborating together via the PI, has found that SHBG is made in brain, may be released in brain, [and] has important very rapid actions on neurons and cells in vitro, and so we would like funding to search for receptors for this potentially very important brain protein. This application proposes a confluence of particular scientific expertise including the PI and Drs. Gustav Jirikowski at the University of Jena, Germany, Jeffrey Tasker of Tulane University and Robert Shapiro at the Oregon Health Sciences University. In the words of one of the reviewers of the initial application, "The mechanism mediating the delivery of steroid hormones to their receptors has important implications for mental health, as well the action of steroid hormones in cancer, heart disease, and other disorders." This proposal examines this mechanism.

Grant:	1R21MH070003-01A1	
Program Director:	WINSKY, LOIS M.	
Principal Investigator:	ARNSTEN, AMY F.T.	PHD
Title:	ESTROGEN, STRESS AND DYSFUNCTION OF PREFRONTAL CORTEX	
Institution:	YALE UNIVERSITY	NEW HAVEN, CONNECTICUT

DESCRIPTION (provided by applicant): Depression and Post-Traumatic Stress Disorder (PTSD) are more prevalent in young women than men. Genetic studies link the CREB1 gene with recurrent depression in women but not men, supporting a neurobiological basis for this gender discrepancy. Both depression and PTSD involve dysfunction of the prefrontal cortex (PFC), a brain region that is 1) critical for regulating behavior, thought and affect, and 2) dysfunctional during exposure to uncontrollable stress. Stress is a major risk factor for depression, and life-threatening stress can cause PTSD. We hypothesize that estrogen promotes

sensitivity to stress, rendering women more susceptible to PFC dysfunction, and thus to stress-related disorders. The proposed research will begin to identify the neurobiological mechanisms through which estrogen exacerbates stress-induced PFC dysfunction. Research in male rats has shown that stress-induced PFC dysfunction arises from excessive catecholamine release in PFC, activating protein kinases A and C, which in turn phosphorylate CREB. Interestingly, alpha-1 adrenoceptors (al R) drive this stress response, while alpha-2A adrenoceptors (a2AR) protect the PFC from stress, and estrogen is known to increase the expression of a1R and reduce the expression of a2AR. Our initial results show that cycling female rats with high levels of circulating estrogen are impaired by mild injection stress, by low doses of a pharmacological stressor, FG7142, and by brief periods of restraint stress which have no effect in males or females with low levels of estrogen. The proposed research will extend these studies to ovariectomized rats with and without estrogen replacement. Aim 1 will test the hypothesis that estrogen amplifies the cognitive and biochemical responses to restraint stress. Biochemical characterization will include measures of a1AR and a2AR expression, catecholamine turnover and phospho-CREB in PFC. Aim 2 will begin to explore the contribution of these biochemical changes to PFC cognitive function, testing whether the increased expression of a1R in the PFC of estrogen-treated rats renders them more sensitive to cognitive impairment. This research will begin to reveal how estrogen amplifies the neurochemical cascades that lead to activation of CREB and dysfunction of the PFC during stress

Grant:	1F32MH070086-01A1	
Program Director:	DESMOND, NANCY L	
Principal Investigator:	JASNOW, AARON M	PHD
Title:	NEUROENDOCRINE MECHANISMS OF EMOTIONAL BEHAVIOR	
Institution:	ROCKEFELLER UNIVERSITY	NEW YORK, NEW YORK

DESCRIPTION (provided by applicant): Natural fluctuations in estrogens have been associated with a number of affective disorders in humans. In particular, low levels of circulating estrogens are associated with increased symptoms of depression, anxiety and cognitive dysfunction, which can often be ameliorated with hormone replacement therapy. Little is known about the mechanisms or the sites of action through which estrogen is influencing emotion, however, they likely occur within the amygdala. Therefore, a comprehensive analysis of the effects of estrogen within the amygdala is needed to further our understanding of how this steroid hormone influences the development of neuropsychiatric disorders in humans. The goal of the current proposal is to (I) determine the genomic and neurochemical actions of estrogen within the amygdala and (II) how they influence fear and anxiety in female rodents. This will be accomplished by examining estrogen-induced changes in gene expression within each region of the amygdala using quantitative-real-time-PCR (Q-PCR). These experiments will be followed by functional studies in which gene function knockdown with a novel antisense oligonucleotide moiety will be used to examine how estrogen-regulated genes influence fear and anxiety. These data will contribute to our knowledge of the hormonal mechanisms underlying fear and anxiety.

Grant:	1F31MH071085-01A1
Program Director:	DESMOND, NANCY L
Principal Investigator:	COFER SMITH, CAROLINE D

BS

Title	ESTROGEN MODULATES HIPPOCAMPAL MORPHOLOGY AND PLASTICITY	
Institution:	UNIVERSITY OF ALABAMA AT BIRMINGHAM	BIRMINGHAM, ALABAMA

DESCRIPTION (provided by applicant): Estradiol (E2) has a role in learning and memory in mammals such as humans, primates and rats. Following the loss of E2, as occurs during aging, the hippocampus, a brain region important for cognition, undergoes alterations in morphology and synaptic transmission. Specifically, CA1 pyramidal cell dendritic spine density and the magnitude of long-term potentiation (LTP) decrease when the levels of E2 decline. I have shown that E2 transiently increases both spine density and LTP magnitude, with LTP returning to control levels prior to spine density. Whether a relationship exists between these two phenomena has not been determined but I have shown that blocking the estrogen-induced increase in spine density blocks the increase in LTP, which suggests these two phenomena are related. The goal of this study is to determine whether the increase in spine density is required for the increase in LTP magnitude, and if spines are necessary, whether the increase in LTP is due to an increase in NMDAR-only spines, termed silent synapses. Elucidating the contribution of E2 to morphology and synaptic plasticity in hippocampus will provide insight into the mechanism by which E2 regulates cognition with age.

National Institute of Neurological Disorders and Stroke (NINDS)

National Institute of Neurological Disorders and Stroke
Menopause-Related Research
FY2004

Molecular Mechanisms of Estrogen Neuroprotection (Wang, K08 NS41342)
Female rats show less brain injury than male rats after an experimentally-induced stroke. However, removing the ovaries from female rats eliminates the protection from stroke-related brain injury, suggesting that female reproductive hormones, such as estrogen, might be neuroprotective. This study focuses on the molecular mechanisms that may contribute to this protective effect.

Hormone Replacement Therapy and Ischemic Stroke Severity (Bushnell, K23NS41929-03)
Animal studies have shown that estrogen reduces stroke severity, but the impact of hormone replacement therapy (HRT) on stroke severity in humans is not known. This observational study seeks to determine if there are differences in stroke severity and outcome based on whether a woman uses HRT or not. To study this question, researchers will record the stroke severity of women admitted to the hospital with acute ischemic stroke, measure differences in markers of the blood coagulation system, and follow the women after the stroke to determine functional and quality of life outcomes. The investigators will then assess whether a prior history of HRT use is correlated with the severity of the initial stroke or with the outcomes after the stroke.

Pharmacologic Plasticity in the Presence of Pain (subproject-Sex Differences and Estrogen Dependency of Spinal Cord Analgesia) (Eisenach/Tobin, P01NS41386) Studies have noted sex differences in analgesic responses to certain painkillers, which may result from higher levels of spinal neuron activity in response to these drugs in females. This group of studies in animals and humans will further examine the neural circuitry involved in chronic pain, and will investigate whether the sex difference in the female response to certain painkillers is dependent on hormones such as estrogen. The overall objective of this project is to better understand chronic pain and to develop improved treatment options.

Epidemiology and Genetics of Parkinson's Disease (Rocca, R01NS33978)
Men are more likely to develop Parkinson's disease (PD) than pre-menopausal women, but the reasons for this sex difference are not fully understood. Hormones such as estrogen could be one factor, since the likelihood of developing Parkinson's disease increases for women after menopause. In addition, postmenopausal women with PD improve with estrogen replacement therapy. These observations suggest that estrogen might influence the survival of the dopamine-containing neurons that degenerate in PD. In this study, the investigators will sample 800 Parkinson's disease (PD) patients and 800 PD-free control subjects. Study participants will be asked about tobacco, coffee and alcohol use. Women will be assessed for estrogen replacement therapy after menopause and other reproductive and estrogen-related factors. The case-control study may confirm preliminary findings on the role of estrogen in PD.

Gender Differences in Cardiac Arrest/CPR (Traystman, R01NS46072)
Despite four decades of research on cardiac arrest and CPR, clinical outcome remains poor. Neurologic and neuropsychologic evaluations of potential differences between men and women after cardiac arrest have not been examined closely. Preliminary findings indicate that brains of females are better protected from cardiac arrest/CPR than males, and that estrogen may be

involved with this neuroprotection. This study will contribute to our understanding of the role of estrogen in neuroprotection, and as a possible therapy for patients of either sex.

Estrogen Modulation of Brain: A-beta Metabolism *in vivo* (Gandy, R01NS41017)
Evidence suggests that estrogen replacement therapy in postmenopausal women appears to reduce the risk of Alzheimer's disease (AD), or delay its onset. However, the mechanism by which estrogen exerts this neuroprotective role is unclear. The investigators will examine the role of estrogen on the release of certain peptides (A-beta) that are aggregated in the brains of individuals with AD. Guinea pigs, transgenic mice and cell cultures will be used to test the effects of estrogen-like drugs on the regulation and metabolism of the A-beta protein.

Ovarian steroid hormones and hippocampal plasticity (Levy, R01NS41582) Estradiol alters the activity of certain neural connections in the brain's hippocampal region. This synaptic plasticity may result in enhanced memory. Estradiol also increases the excitability of neurons in the hippocampus, and may cause changes in synaptic plasticity in this brain region. Using appropriate testing methods in rats, the investigators will measure the effect of estradiol on the excitability of hippocampal neurons, and ascertain whether synaptic plasticity is increased over time. This study will provide important insights for understanding the biological basis for memory problems that can occur with menopause.

Estrogen, BDNF and hippocampal hyperexcitability (Scharfman R01NS037562)
The central hypothesis of this proposal is that estrogen induces the expression of brain derived neurotrophic factor (BDNF) in the brain's hippocampus, and this leads to changes in neuronal excitability that ultimately increase the susceptibility to seizures. This hypothesis is relevant to women with epilepsy, including those with catamenial epilepsy, or those taking estrogen. Experiments to measure neuronal excitability will be conducted using rats at various stages of the estrus cycle, and using ovariectomized rats with and without hormone replacement.

Neuromodulation of reproduction during aging (Gerhold F31NS047875)
The brain plays a critical role in the aging of the reproductive system. A small region of the brain's hypothalamus is essential in providing time-of-day information needed to maintain normal surges of reproductive hormones, including gonadotropin releasing hormone (GnRH) and leutinizing hormone (LH). This study will investigate the neuronal activity that controls hormonal surges of GnRH and LH, and assess the effects of age on these processes. This research will enhance our understanding of factors that influence the menopausal transition.

Estrogen: neuroprotection and rescue (Zukin, R01NS045693)
Estrogen appears to protect neurons against damage caused by lack of oxygen, or ischemia, as can occur during a heart attack or stroke. Studies in animals have suggested that long-term treatment with estrogen can improve the survival rates of neurons exposed to ischemic conditions. The objective of this basic study is to identify the ways in which estrogen acts to protect neurons from damage in an animal model of ischemia.

Hormones and biomarkers predicting stroke in women (Wassertheil-Smoller R01NS042618)
The Women's Health Initiative clinical trial of estrogen plus progestin for the prevention of cardiovascular disease in healthy, postmenopausal women found increased risk of stroke in users of estrogen plus progestin. This study will investigate possible reasons for the increased risk of stroke by studying biomarkers of blood clot formation and inflammation. This population based

nested case-control study will compare biomarkers in 1050 ischemic stroke cases and 1050 matched controls, drawn from the participants in the Observational Study component of the Women's Health Initiative (WHI-OS).

Pathophysiology of HIV dementia in women (Wojna S11NS046278)
The population of women with AIDS is increasing as a consequence of changes in the epidemiology of HIV infection. HIV associated dementia (HAD) continues to be one of the major complications of AIDS and little is known about hormonal modifiers, which can impact on the development and severity of HAD in women. This cross sectional study will identify HIV infected women at high risk of developing HAD and will determine if gonadal dysfuction and oxidative stress contribute to the dementia.

Beta endorphin neurons and the control of homeostasis (Kelly R01NS038809)
Estrogen influences homeostatic functions like temperature regulation, stress responses, feeding, motivation and reward. Selective estrogen receptor modulators (SERMs) that produce the beneficial effects of estrogen in the central nervous system but lack the adverse effects of traditional hormone replacement therapy are greatly needed. These studies will not only identify the pathway(s) critical for rapid estrogen signaling in beta endorphin neurons but also may allow the development of new SERMs specifically targeting critical brain circuits involved in the control of homeostasis in the female.

Neural control of temperature regulation (Boulant R01NS014644)
Networks of neurons in the brain's hypothalamus regulate body temperature and fever. Neurons in this region integrate information from the external and internal environment to generate changes in skin blood flow, sweating, and shivering. It is likely that this network is also affected by reproductive hormones, causing menopausal hot flashes and changes in body temperature during the menstrual cycle. This study will characterize these neurons and investigate how they form a connected network to control thermoregulatory responses.

***In vitro* studies of steroid receptors in NF1** (Fishbein F30NS043951)
Neurofibromatosis type I (NF1) is characterized by abnormal proliferation of cells in tumors known as neurofibromas. Neurofibromas are often aggravated during puberty and pregnancy, suggesting an altered sensitivity to steroid hormones. These studies will characterize the role of hormones in neurofibroma development, allowing patients with NF1 and their physicians to make more educated medical decisions about hormone therapies for birth control, menopause, or disease treatments.

Study of tumor growth and cyst development in von Hippel Lindau disease (NINDS Intramural program, Protocol Number: 00-N-0140)
Patients with von Hippel-Lindau (VHL) disease develop cysts or tumors of the cerebellum, brainstem and spinal cord, as well as in other areas of the body. This study seeks to identify factors that predict or influence tumor progression or cyst development in order to better inform treatment decisions. Information will be prospectively collected about processes that may influence tumor progression in women, such as puberty, menopause, pregnancy, and effects of hormone therapy.

Sex and gene expression conference (Sandberg R13NS048416)

This grant provided partial funding support for the fifth annual Sex and Gene Expression Conference (SAGE V), held March 18- 21, 2004. The primary goal of this conference was to explore the interaction between biological sex and genetic expression throughout the lifespan. The conference session topics included sexual dimorphism in the brain, the biology of aging, and gonad development, physiology and disease.

National Institute of Nursing Research (NINR)

National Institute of Nursing Research
2004 Menopause Related Grants

Grant Number	*Title*	*Principle Investigator*	*Institution*
2P30NR005051-06	Hormone Replacement Therapy Among Women with Disabilities	Becker, Heather	University of Texas Austin
1R15NR008003-01A2	Nursing Interventions for Symptoms of Perimenopause	Berg, Judith	University of Arizona
5R01NR007738-02	Home vs. Center-Based Weight Loss and Exercise in Menopause	Dennis, Karen	University of Central Florida
5R01NRNR005339-05	Estrogen/Platelet Interaction in Cerebral Ischemia	Kearney, Marguerite	Johns Hopkins University
5R01NR004141-09	Menopausal Transition: A Biobehavioral Model of Symptoms	Mitchell, Ellen	University of Washington
5R01NR005281-04	Heart Disease in Women: Estrogen Effects on Hemodynamics	Sherwood, Andrew	Duke University
2U01NR004061-10A1	The Study of Women's Health Across the Nation-Michigan	Sowers, MaryFran	University of Michigan at Ann Arbor
5R01NR004861-04	Promoting Healthy Eating and Activity in Rural Women	Walker, Susan	University of Nebraska Medical Center
5R01NR007743-03	Prevention of Osteoporosis in Breast Cancer Survivors	Waltman, Nancy	University of Nebraska Medical Center

National Institute of Nursing Research
Menopause Related Grants
FY 2004

Summary of Current NINR Grants Relevant to Menopause

Hormone Replacement Therapy (HRT) among Women with Disabilities (Becker-NR005051).
This study compares factors that women with physical disabilities consider when addressing decisions about HRT and aspects of decision making. Findings to date show that many women with disabilities do not know about HRT effects, and would like more tailored information. Provider recommendation and willingness to comply with that recommendation were the strongest predictors of HRT use for this population. Findings from this research will add to the limited but growing body of knowledge regarding the menopausal health needs of disabled women.

Nursing Interventions for Symptoms of Perimenopause (Berg-NR008003).
Increasingly, women are choosing alternatives to hormone replacement therapy (HRT) for symptom management during the perimenopausal transition, although effectiveness of these alternatives have not been well studied. NINR funded researchers employing a longitudinal repeated measures randomized three-group design: (a) multimodal treatment package (high fiber, low-fat diet; moderate exercise; stress reducing techniques), (b) soy isoflavone capsules, and, (c) a control condition - are investigating their effectiveness at managing severe perimenopausal symptoms. The information gleaned from this pilot study will inform a larger intervention trial.

Home vs. Center Based Weight Loss and Exercise in Menopause (Dennis-NR007738).
Evidence suggests that multi-faceted obesity treatment promotes the best weight loss outcomes, however the most effective site and methods for treatment delivery and follow-up care remain unknown. The researchers will test the efficacy of a HOME vs. CENTER-based diet and exercise intervention for postmenopausal women. Findings may help to identify best practice care for obese, sedentary, and postmenopausal women.

Estrogen/Platelet Interaction in Cerebral Ischemia (Kearney-NR005339).
Research shows that premenopausal women are at a lower risk for CVD when compared with men. Researchers are clarifying the role of exogenous estrogen therapy in ischemic brain injury both mechanistically and according to dosage. Findings may help to clarify the role of estrogen as a potential therapy for both genders.

Menopausal Transition: A Biobehavioral Model of Symptoms (Mitchell-NR004141).
Although information related to the science of menopause is accruing, little remains known about the natural history of the menopausal transition, particularly the years prior to menopause. NINR funded researchers are continuing to build on their longitudinal description of the early, middle and late stage of the menopausal transition in a group of midlife women. Measures include hormone changes, perceived stress, physiologic stress arousal, symptoms, and depressed mood during three stages of the menopausal transition. Additionally, the study will investigate the effects of genetic polymorphisms of the estrogen receptor gene and estrogen metabolic genes on estradiol and estrone levels, age of onset of middle and late transition and menopause, and menstrual bleeding.

Heart Disease in Women: Estrogen Effects on Hemodynamics (Sherwood-NR05281).
Coronary heart disease (CHD), the leading cause of death in women in the U. S., increases rapidly following menopause when estrogen levels decline. Researchers are examining the acute effects of estrogen and estrogen/progesterone on vascular endothelial function and on peripheral vascular resistance

in postmenopausal women with a history of CHD. Information derived for this study could enhance our understanding of how HRT may alter risk in CHD.

The Study of Women's Health Across the Nation (SWAN) (Sowers-NR004061).
Funded in September 1994 by NINR and NIA, with support from the ORWH, OBSSR, NICHD, NIMH, NCMHD, and NCCAM, SWAN is a multidisciplinary epidemiological study of the natural history of menopause, designed to characterize menopause in terms of ovarian aging, risk factors symptoms, cardiovascular risk, and bone health in an ethnically diverse sample (African- Americans, Caucasians, Chinese, Hispanics, and Japanese). NINR funds the clinical site at the University of Michigan where the investigator is examining menopausal related changes in a sample of more than 320 African-American and 220 Caucasian women age 40-55. Women are being followed longitudinally for changes in such variables as joint health, bone density and body composition. This is one of the first epidemiological studies to examine the menopausal effects in perimenopausal women of 5 ethnic groups.

Promoting Healthy Eating and Activity in Rural Women (Walker-NR004861).
Although women's health risks increase at menopause, chronic diseases, associated disabilities and increased economic costs are not unavoidable consequence of aging. Employing a longitudinal randomized control trial, NINR funded researchers are investigating the impact of an individualized/tailored intervention based upon a Health Promotion Model (HPM) to a standard non individualized intervention focused on the initiation and maintenance of physical activity and health eating habits. Outcomes include both behavioral measures and biological markers and findings have the potential to make a substantial contribution to the literature on the initiation and maintenance of health lifestyle behaviors.

Prevention of Osteoporosis in Breast Cancer Survivors (Waltman-NR007743).
A substantial percentage of women with breast cancer have estrogen receptor positive tumor status and are therefore ineligible for hormone replacement therapy. These women are particularly vulnerable to osteoporosis since without estrogen, bone loss occurs rapidly the first five years of menopause onset and continues over time, albeit at a slower rate. NINR funded researchers are investigating whether strength/weight training exercises enhance the effectiveness of risedronate (5 mg/day), calcium (1200 mg/day), and vitamin D (400 IU/day) in improving bone mineral density (BMD) in post-menopausal breast cancer survivors. Findings from this study have the potential to provide evidence of an effective alternative to HRT for treatment of osteoporosis in breast cancer survivors who ineligible for HRT.

Summary of Published NINR Findings Relevant to Menopause

Dormire SL, Reame NK. (2003). Menopausal hot flash frequency changes in response to experimental manipulation of blood glucose. *Nursing Research*, 52 (5): 338-343.

Primary Question: Is there a significant difference in the incidence of menopausal hot flashes between conditions of fasting and experimentally sustained blood glucose concentrations?

Summary of Findings: Hot flashes are a frequently reported symptom of menopause, generally associated with declining estrogen levels. Postmenopausal women on hormone replacement therapy were asked to stop their medication and maintain a diary of hot flash frequency. When frequency was at least 4 times per day, the women were admitted to a research center, and their blood glucose levels were manipulated by IV infusions. There was a significant reduction in hot flashes when the women had elevated blood glucose levels similar to those found after a meal. Fasting may trigger the mechanism for menopausal hot flashes.

Sternfeld B, Wang H, Quesenberry Jr. CP, Abrams B, Everson-Rose SA, Greendale GA, Matthews KA, Torrens JI, & Sowers M. (2004). Physical activity and changes in weight and waist circumference in

midlife women: findings from the Study of Women's Health Across the Nation. *American Journal of Epidemiology*, 160 (9): 912-922.

Primary Question: Are changes in body weight and fat deposition in midlife women related to menopause, or are they consequence of the normal aging process?

Summary of Findings: Using data from the Study of Women's Health Across the Nation (SWAN), researchers analyzed the patterns of change in weight, waist circumference, activity level, and exercise for over 3,000 premenopausal or early perimenopausal women. Over the 3-year study period, the averages for both body weight and waist circumference increased by 3%. There were no differences in weight gain or waist circumference related to menopause status. However, women who participated in sports or exercise or increased their daily routine activities demonstrated a slower gain or even a decrease in weight. Physical activity, both through specific exercise and as part of an active lifestyle, can help midlife women maintain a healthy weight.

Berman DM, Nicklas BJ, Ryan AL, Rogus EM, Dennis KE, Goldberg AP. (2004). Regulation of lipolysis and lipoprotein lipase after weight loss in obese, posmenopausal women. *Obesity Research*, 12 (1): 32-39.

Primary Question: Will a low calorie and a low-intensity walking exercise program affect the regulation of lipolysis in obese, postmenopausal women?

Summary of Findings: The metabolic effects of a low calorie and exercise program were measured for obese, post-menapausal women in relation of a low calorie diet and low-intensity exercise. Responsiveness to basal lipolysis was greater in abdominal fat cells than in gluteal fat cells, but there were no differences in postreceptor-stimulated lipolysis, plasma triglycerides, or HDL-C levels. Weight loss in these women does not affect regional fat metabolism and may predispose them to develop abdominal fat.

Sowers M, Derby C, Jannausch ML, Torrens JI, Pasternak R. (2003). Insulin resistance, hemostatic factors, and hormone interactions in pre-and perimenopausal women: SWAN. *The Journal of Clinical Endocrinology & Metabolism.* 88 (10): 4904-4910.

Primary Question: Are reproductive hormones in women, including FSH, estradiol, and testosterone, associated with clotting factors and insulin resistance?

Summary of Findings: The role that female reproductive hormones play on reducing the incidence of heart disease in women by minimizing thrombosis remains unclear, but insulin resistance may be one contributing factor. As part of the Study of Women's Health Across the Nation (SWAN), hormone concentrations, clotting factors, and insulin and glucose levels were measured for over 3,000 midlife women. As expected, pre- and perimenopausal women with diabetes had higher insulin values and insulin resistance, a higher body mass index, and elevated clotting factors, compared to women without diabetes. Sex hormone binding globulin (SHBG) was inversely associated with insulin resistance, and dampened the relationship between clotting factors and insulin resistance.

Santoro N, Lasley B, McConnell D, Allsworth J, Crawford S, Gold EB, Finkelstein JS, Greendale GA, Kelsey J, Korenman S, Luborsky JL, Matthews K, Midgley R, Powell L, Sabatine J, Schocken M, Sowers MF, Weiss G. (2004). Body size and ethnicity are associated with menstrual cycle alterations in women in the early menopausal transition: The Study of Women's Health across the Nation (SWAN) Daily Hormone Study. *The Journal of Clinical Endocrinology & Metabolism.* 86 (6): 2622-2631.

Primary Question: What are the baseline biological and demographic characteristics and daily hormonal patterns of the menstrual cycles of midlife women from different ethnic groups in the United States?

Summary of Findings: The Daily Hormonal Study was a subset of the Study of Women's Health Across the Nation (SWAN) involving over 800 women who collected first-void urines daily for one complete menstrual cycle, or for 50 days in the absence of menstruation. Over 80% of the cycle specimens showed evidence of luteal activity indicating continued hormone production. Women who were 49 years of age or older were had more irregular cycles and less luteal activity, while women with a lower body mass index

had shorter cycles and higher hormone levels. Chinese- and Japanese-American women had lower estrogen excretions. Smoking did not affect cycle length or hormone concentrations. The findings suggest that the ovary remains sensitive to elevated follicle stimulating hormone in the early menopause transition.

Sampselle CM, Harris V, Harlow SD, Sowers M. (2002). Midlife development and menopause in African American and Caucasian women. *Health Care for Women International*, 23: 351-363.

Primary question: What are the meanings that midlife women attach to the menopause transition, and do these differ between White and Black women?

Summary of findings: For midlife women, mental health care assessments have often focused on issues relating to the menopause transition, ignoring broader developmental and lifestyle changes. From focus group discussions with midlife women, most identified major life milestones relating to child bearing and rearing, mortality, changing family relationships, increasing self-efficacy, and life experiences, while few mentioned menopause. Many women felt that their turn had come to pursue their own interests. Black women tended to note menopause as a normal phase of life, while White women focused more on the signs of aging. Those past menopause often expressed relief at the freedom it brought.

Sampselle CM, Harlow SD, Skurnick J, Brubaker L, Bondarenko I. (2002). Urinary incontinence predictors and life impact in ethnically diverse perimenopausal women. *Obstetrics & Gynecology*, 100 (6): 1230-38.

Primary question: What is the prevalence, associated risk, and the daily impact of mild to severe urinary incontinence among perimenopausal women?

Summary of findings: While urinary incontinence (UI) is estimated to affect one third of older women in the US, little is known about its cause, range of severity, or difference in prevalence among different ethnic groups. Using survey data from the Study of Women's Health Across the Nation (SWAN), researchers found that over half of perimenopausal women had experienced UI, with one-quarter reporting moderate to severe leakage. White women experienced the highest incidence, and Hispanic women the lowest. Associated risk factors included parity, perimenopausal status, diabetes, obesity, and current smoking. The high incidence of UI warrants screening among midlife women.

Glazer G, Zeller R, Delumba L, Kalinyak C, Hobfoll S, Winchel, J, Hartman P. (2002). The Ohio Midlife Women's Study. *Health Care for Women International*, 23: 612-630.

Primary question: How do menopause symptoms and menopause status, attitudes, coping, and demographic characteristics affect health-promoting activities for White and Black women in the United States?

Summary of findings: The Ohio Midlife Women's Study followed both pre- and post-menopausal women around the time of the menopause transition. Results found that roughly one third showed signs of anxiety, and one quarter suffered from depression, with the highest levels occurring around the onset of menopause. However, menopause status itself was not related to anxiety or depression. Common menopause symptoms included loss of energy, irritability, tension, headaches and joint pain, and trouble sleeping. Higher educational levels, more effective coping, and a more positive attitude towards menopause helped to enhance health promoting behaviors such as exercise, nutrition awareness, and self-actualization. Stress was more strongly related to health outcomes and behaviors than menopause status.

Villarruel AM, Harlow SD, Lopez M, Sowers MF. (2002). El cambio de vida: conceptualizations of menopause and midlife among urban Latina women. *Research and Theory for Nursing Practice: An International Journal*, 16 (2): 91-102.

Primary question: What are the experiences of Latina women in the United States?

Summary of findings: Menopause, a vital life-cycle phase for women, is imbued with many personal, social, and cultural meanings. In focus group interviews, older Latina women discussed the role that

menopause played in their lives. Three common themes emerged: 1) menopause can reorder the harmony and balance in life, 2) the "change of life" is a normal adult phase that women must pass through, and 3) this period is a time for women to reorient their lives to focus more on personal needs and desires. However, many women lacked basic knowledge about the course of menopause and possible ways to manage symptoms. In general, the women described menopause as a social and cultural phenomenon bringing an important change in their life, but many also expressed a need for more information.

National Center for Complementary and Alternative Medicine

(NCCAM)

NCCAM NIH Research and Other Efforts Related to Menopausal Transtition

The mission of the National Center for Complementary and Alternative Medicine (NCCAM) is to explore complementary and alternative healing practices in the context of rigorous science; to train CAM researchers; and to disseminate authoritative information to the public and professionals. The list of CAM practices and therapies will change as some are proven to be safe and effective and become accepted as "mainstream" health care practices. NCCAM groups CAM practices within five major domains: (1) whole medical systems (i.e., traditional Chinese medicine, naturopathic medicine, Ayurveda); (2) mind-body medicine (i.e., meditation, biofeedback); (3) biologically based practices (i.e., herbal therapies, special diets); (4) manipulative and body-based practices (i.e., chiropractic, massage); and (5) energy medicine (i.e., reiki, qi gong). NCCAM conducts and supports basic and applied (clinical) research and research training within these five areas.

NCCAM has a strong interest in menopausal health because of the number of CAM modalities being used by peri- and post-menopausal women to treat a range of symptoms. In the wake of the Women's Health Initiative, aggressive marketing campaigns are encouraging use of CAM products for menopausal symptoms, and the level of use is likely to increase. According to longitudinal survey data from the Study of Women's Health Across the Nation (SWAN), almost 50% of peri- and post-menopausal women had used CAM therapies in the past year. NCCAM continues to provide support for SWAN to continue data collection related to CAM use and the menopausal transition.

NCCAM has taken a multi-pronged approach to improving our knowledge of CAM for the treatment of menopausal symptoms, convening workshops, producing reports, and supporting research and research training. For example, in January 2004, NCCAM, in collaboration with ORWH and several other NIH Institutes and Centers (ICs), convened a workshop to assess the quality of measures of hot flashes. (A summary of that workshop is available on the NCCAM website at http://nccam.nih.gov/health/hotflashes/hotflash_summ.htm) Critical to the evaluation of treatment efficacy is the quality of outcome measures. However, when objective measures (i.e., sternal skin conductance) are compared with self-reported measures taken under ambulatory conditions, women significantly under-report the frequency of hot flashes. In September 2004, NCCAM, along with NIA, NIBIB, and ORWH, issued an RFA for SBIR applications to improve sternal skin conductance technologies to facilitate long-term data collection on hot flash frequency under ambulatory conditions. We expect to make approximately five awards in FY 05.

NCCAM will also join NIA in sponsoring a state-of-the-science conference on the management of menopause related symptoms, which will be convened in March 2005. This meeting will assess a range of therapies used to treat menopausal symptoms, including CAM modalities.

In response to concerns raised about the safety of black cohosh, an herbal dietary supplement used to treat menopausal symptoms, NCCAM and the Office of Dietary Supplements convened a workshop in November 2004. NCCAM and other ICs participating in the workshop support clinical research on black cohosh. First and foremost is our concern for the safety of research subjects. Given ambiguity and uncertainty in the scientific literature, we wondered what additional actions if any NIH needed to take to protect participants in research. That workshop reviewed what is known about purported estrogenic activity of black cohosh, its effect on breast

and prostate tissue, data from a murine model suggesting an increased incidence of metastatic lesions from breast to lung among animals fed black cohosh, and several cases of hepatotoxicity alleged to be connected to use of this dietary supplement. When the workshop report is completed, it will be available on the NCCAM website at http://nccam.nih.gov/.

NCCAM supports a range of research projects on menopause, through individual grants and centers. Some of this research will provide much-needed information on the safety and efficacy of a number of CAM therapies used for menopausal symptoms while more basic research will provide valuable information on active ingredients, mechanisms of action, and the like. For example, ongoing basic research is looking at the effect of black cohosh extract on human breast tissue and the role of *Cimicifuga racemosa* as a serotonin modulator. A recently funded study is using molecular biology techniques to identify herbs that exhibit selective estrogenic activity for estrogen receptor beta, which appears to inhibit proliferation and breast tumor formation in mouse xenografts and thus presents a potentially safer treatment for menopausal symptoms than estrogen. And another recently funded study will collect plant specimens used for menopausal symptoms by indigenous populations in Guatemala and Costa Rica, make extracts from those plants, elucidate active constituents, and conduct bioassays to assess estrogenic and serotonergic activity and antioxidant effects. A new research training grant will look at the mechanisms by which black cohosh and red clover affect neurocognitive function and mood, using magnetic resonance imaging, diffusion tensor imaging, and other cutting-edge methodologies.

Ongoing clinical research on menopause targets several CAM botanical therapies, including black cohosh, red clover, soy and other phytoestrogens, as well as the use of non-botanical treatments (e.g., therapeutic touch, macrobiotic diet) to deal with a range of symptoms, such as hot flashes, osteoporosis, and cognitive and affective problems. Examples of more clinically oriented research include a study on the impact of phytoestrogens on cognition, affect, and atherosclerosis and an epidemiologic study of the influence of soy consumption on menopause in Japan. The Center on Botanical Dietary Supplements for Women's Health in Chicago, supported by the Office of Dietary Supplements (ODS) and NCCAM, is completing studies on the clinical safety and efficacy of botanicals used to treat women's health with particular emphasis on therapies for menopause. Projects are preparing standardized dietary supplements, isolating active compounds for structure elucidation, and determining the mechanism of action and efficacy of several botanicals (i.e., black cohosh and red clover) used for menopausal symptoms, including hot flashes, bone turnover, and vaginal dryness. Work at another ODS/NCCAM-funded Center, the Botanical Center for Age-Related Diseases in Indiana, focuses on characterizing active ingredients in botanicals. The emphasis there is on determining the efficacy of polyphenolic compounds in reducing risk of age-related diseases including osteoporosis, cancer, cardiovascular disease, and neurodegeneration. Specific projects will study isoflavones and bone resorption in postmenopausal women, the effects of soy isoflavones on prostate, breast and bone, and soy and estrogen interactions on breast and endometrium markers.

National Center for Research Resources (NCRR)

National Center for Research Resources

Menopause Related Research

The National Center for Research Resources (NCRR) develops and supports critical research technologies that underpin health-related research to maintain and improve the health of our Nation's citizens. NCRR supports shared resources, sophisticated instrumentation and technology, animal models for study of human disease, clinical research, and research capacity building for underrepresented groups.

Through its support of multidisciplinary research, NCRR is uniquely positioned to provide either primary research support or provide resource support in partnership with other Institutes or Centers to address emerging clinical and basic research needs, such as the study of menopause. Expansion of NCRR's present efforts in new biotechnologies and instrumentation, development of animal models, and clinical research will foster interdisciplinary collaborations and advance NIH's efforts to study menopause, as evidenced by the examples of on-going research that is cited below.

Selective Estrogen Receptor Modulators improve cardiovasuclar function in menopause-induced rat model

During menopause, women have a higher propensity for developing cardiovascular disease. Studies have shown that treatment with selective estrogen receptor modulators (SERMS) improves cardiovasuclar status in menopausal women. The mechanisms involved, however, have not been elucidated. Researchers at the University of Puerto Rico Medical Sciences campus, with funding from the NCRR Research Centers in Minority Institutions (RCMI) Program, evaluated the effect of toremifene, a new member of the SERM family, on the cardiovascular status of an ovariectomized rat model. In these experiments, systolic blood pressure, plasma nitric oxide and estradiol levels, aortic wall thickness, and cholesterol profiles were determined after treatment with toremifene. After 4 weeks of treatment, a marked improvement in the cardiovascular status of menopause-induced rats was observed as evidenced by decreased blood pressure, restoration of smooth muscle function and structure in vascular walls, and modified serum lipid profiles. This study provides evidence that toremifene may be beneficial to the cardiovascular system following menopause in this animal model.

Jorge Gonzalez-Perez and Maria Crespo. Chronic Effects of toremifene on the vasculature of menopause-induced rats. Vascular Pharmacology. 40:261-268 (2004).

Insulin, physical activity, and caloric intake in postmenopausal women: breast cancer implications

Increased physical activity and programs to reduce body mass index (BMI) with both increased physical activity and decreased caloric intake have been proposed to reduce insulin as a potential mediator of breast cancer and other chronic diseases. Researchers at the Los Angeles Biomedical Research Institute at Harbor-UCLA, selected an ethnically diverse subsample of 2,996 mostly healthy postmenopausal women with no prior cancer history from the participants in the Women’s Health Initiative clinical trials and observational study. Information was collected on diet, recreational physical activity, and BMI. Using a cross-sectional design, insulin levels were compared across quintiles of caloric intake and physical activity. Lower BMI, lower caloric intake, and higher levels of physical activity were all independently associated with lower mean fasting insulin levels. These findings suggest that reduction in BMI achieved through

increasing physical activity, reducing caloric intake, or both, should lower insulin levels, providing support for clinical trials evaluating insulin level change and breast cancer risk.

R.T. Chlebowski, M. Pettinger, M.L. Stefanick, B.V. Howard, Y. Mossavar-Rahmani, and A. McTiernan. Journal of Clinical Oncology. 22(22):4507-4513 (2004).

Mechanism of increased bone loss after menopause

Loss of bone density after menopause is a well-known risk factor for fractures. The mechanisms are known to involve reduced levels of estrogen in the blood that allow increased bone breakdown. The cells that make and break down bone are controlled by several locally-acting hormones called paracrine mediators, of which RANKL is the final common pathway. Researchers at the Mayo Clinic, with support from the NCRR, isolated cells from the bone marrow of premenopausal and postmenopausal women who were, or were not, taking an estrogen replacement. The marrow cells were tested for RANKL on their surfaces. The surface concentration of RANKL per cell was highest in the untreated compared with the estrogen-treated postmenopausal women and the premenopausal women. These data are consistent with the view that an increase in RANKL expression on bone marrow cells is an important determinant of increased bone breakdown induced by estrogen deficiency. This information on the cell and molecular biology underlying changes in bone density may lead to future treatments to reduce the risk of bone fractures in postmenopausal women.

Guitty Eghbali-Fatourechi, Sundeep Khosla, Arunik Sanyal, William J. Boyle, David L. Lacey and B. Lawrence Riggs. Role of RANK ligand in mediating increased bone resorption in early postmenopausal women J. Clin. Invest. 111:1221-1230 (2003).

Walking to control weight among overweight and obese post menopausal women

Obesity is increasingly common and is accompanied by increases in the prevalence of diabetes, hypertension and cardiac disease. Exercise is known to contribute to weight loss, but the duration and kind of exercise have not been defined. Researchers at the University of Washington Clinical Research Center, with funding from the NCRR, participated in a study that sought to determine whether the equivalent of three hours of brisk walking per week would affect weight and intra-abdominal body fat. The study took the form of a randomized controlled trial (conducted from 1997 to 2001) of 173 sedentary, overweight postmenopausal women aged 50 to 75 years who were living in the Seattle area. One group of 87 women participated in moderate-intensity sports and recreational activity for a mean of 3.5 days/wk for 176 min/wk. Walking was the most frequently reported activity. After 12 months, the exercisers were an average of 1.4 kg lighter than the 86 women who performed only stretching exercises. The exercise group also lost about 1.0% of their total body fat. Greater body fat loss was observed with increasing duration of exercise. The researchers concluded that regular exercise such as brisk walking results in reduced body weight and body fat among overweight and obese postmenopausal women.

Melinda L. Irwin, PhD, MPH; Yutaka Yasui, PhD; Cornelia M. Ulrich, PhD; Deborah Bowen, PhD; Rebecca E. Rudolph, MD, MPH; Robert S. Schwartz, MD; Michi Yukawa, MD; Erin Aiello, MPH; John D. Potter, MD, PhD; Anne McTiernan, MD, PhD. Effect of Exercise on Total and Intra-abdominal Body Fat in Postmenopausal Women. A Randomized Controlled Trial JAMA. 289:323-330 (2003).

Hormone Replacement Therapy and Metabolic Cardiovascular Risk

After menopause, women gain body fat particularly in the intra-abdominal cavity and become less sensitive to insulin, increasing their risk of developing diabetes mellitus and cardiovascular disease. Investigators at the University of Vermont have sought to determine whether hormone replacement therapy reduces intra-abdominal and subcutaneous abdominal fat and improved insulin sensitivity in postmenopausal women. In the 2-year randomized, double-blind placebo-controlled trial 76 women received conjugated estrogens (0.625 mg) plus progesterone at baseline, 6 months, 1 year, and 2 year time points. DEXA scan was used to determine body composition, and a euglycemic hyperinsulinemic clamp was used to measure insulin sensitivity. The investigators found that HRT did not have an effect on intra- abdominal fat, subcutaneous abdominal fat, total fat, percent fat, lean body mass, or weight. However, insulin sensitivity decreased significantly in the HRT group compared to the placebo group ($p=0.02$). The study conclusions suggest that estrogen plus progestin replacement therapy reduces insulin sensitivity without affecting body composition or body fat distribution.

C.K. Sites, M.J. Toth, M. Cushman, G.D. L'Hommedieu, A. Tchernof, R.P. Tracy, E.T. Poehlman. Menopause-related differences in inflammation markers and their relationship to body fat distribution and insulin-stimulated glucose disposal. Fertil Steril. 77:128-135 (2002).

Effects of estrogen replacement therapy on bone turnover in ovariectomized cynomolgus monkeys.

Over the past 9 years, the investigators have developed and analyzed a monkey model of menopause, particularly as is relates to conditions affecting the skeletal system. Ovariectomized cynomologus monkeys develop osteoporosis and osteoarthritis, similar to post-menopausal women. Most recently, the investigators have examined the effects of estrogen replacement therapy on subchondral bone of the proximal tibia in these animals. The subchondral bone directly underlies the articular cartilage and previous studies suggest that changes in this area of bone affects the health of the overlying cartilage, and thus the potential severity of osteoarthritis. The current studies show that bone turnover is decreased by estrogen replacement therapy and also that soy phytoestrogens help preserve bone volume in the absence of estrogen. The monkey model can thus be used to examine many aspects of the physiological effects of estrogen replacement therapy on the skeletal system during menopause.

K.D. Ham and C.S. Carlson, "Effects of estrogen replacement therapy on bone turnover in subchondral bone and epiphyseal metaphyseal cancellous bone of ovariectomized cynomolgus monkeys. J. of Bone and Mineral Research.19: 823-829 (2004).

NCRR MENOPAUSE RESEARCH RELATED GRANTS – FY 2002-2004

GRANT NUMBER	TITLE	PI	INSTITUTION
G12 RR003051	ACT 5 III: WOMEN HEALTH: MENOPAUSE & HEALTH IN HISPANIC WOMEN IN PUERTO RICO	ROMAGUERA, JOSEFINA	UNIVERSITY OF PUERTO RICO MED SCIENCES
G12 RR013646	P2: ESTROGEN REPLACEMENT THERAPY & NEURON STRUCTURE: ALZHEIMERS	CLAIBORNE, BRENDA J	UNIVERSITY OF TEXAS SAN

			ANTONIO
K01 RR000170	NON HUMAN PRIMATE MODEL OF NATURAL MENOPAUSE CARDIOVASCULAR DIS OSTEOPOROSIS	HONORE, ERIKA K	SOUTHWEST FOUNDATION FOR BIOMEDICAL RES
K23 RR016067	WOMEN AT HIGH RISK FOR CAD AFTER MENOPAUSE: BENEFITS OF ERT	CARR, MOLLY C	UNIVERSITY OF WASHINGTON
K23 RR016321	POSTMENOPAUSAL HORMONAL REPLACEMENT THERAPY SYMPATHIC NERVE & HYPERTESION	VONGPATANASIN, WANPEN	UNIVERSITY OF TEXAS SW MED CTR/DALLAS
K23 RR017043	NEUROBIOLOGICAL EFFECT OF LONG-TERM ESTROGEN REPLACEMENT	SMITH, YOLANDA R	UNIVERSITY OF MICHIGAN AT ANN ARBOR
M01 RR000030	HEART DISEASE IN WOMEN: ESTROGEN EFFECTS ON HEMODYNAMICS	SHERWOOD, ANDREW	DUKE UNIVERSITY
M01 RR000032	POST MENOPAUSAL HORMONE THERAPY	GOWER, BARBARA	UNIVERSITY OF ALABAMA AT BIRMINGHAM
M01 RR000034	IMPACT OF ENZYME-INDUCING ANTIEPILEPTIC DRUGS ON HORMONE REPLACEMENT THERAPY	MCAULEY, JAMES W	OHIO STATE UNIVERSITY
M01 RR000037	FOLLICLE DEVELOPMENT STUDY	KLEIN, NANCY	UNIVERSITY OF WASHINGTON
M01 RR000037	ESTROGENS, BODY FAT AND DYSLIPIDEMIA AT MENOPAUSE	CARR, MOLLY	UNIVERSITY OF WASHINGTON
M01 RR000037	SLEEP IN OLDER WOMEN: EFFECTS OF ESTROGEN	MOE, KAREN	UNIVERSITY OF WASHINGTON
M01 RR000037	EXERCISE EFFECTS ON HORMONES IN POST-MENOPAUSAL WOMEN	MCTIERNAN, ANNE	UNIVERSITY OF WASHINGTON
M01 RR000040	THE EFFECTS OF ESTROGEN AND DHEA SUPPLEMENTATION ON SERUM LIPIDS, & MUSCLE MASS	BARNHART, KURT	UNIVERSITY OF PENNSYLVANIA
M01 RR000040	NMR IMAGING AND STEROLOGIC ANALYSIS OF TRABECULAR BONE	WEHRLI, FELIX	UNIVERSITY OF PENNSYLVANIA
M01 RR000042	ROLE OF GLUCOSE IN MENOPAUSAL HOT FLASHES	DORMIRE, SHARON L	UNIVERSITY OF MICHIGAN AT ANN ARBOR
M01 RR000042	SAFETY OF ESTROGENS IN LUPUS ERYTHEMATOSUS NATIONAL ASSESSMENT (SELENA)	MCCUNE, WILLIAM J	UNIVERSITY OF MICHIGAN AT ANN ARBOR
M01 RR000042	EFFECT OF TRANSDERMAL ESTROGEN & ORAL ISOFLAVONE ON SEX HORMONE-BINDING GLOBULIN	LEE, CATHY C	UNIVERSITY OF MICHIGAN AT ANN ARBOR

M01 RR000042	THE ROLE OF HYPOTHALAMIC AGING IN MENOPAUSE	REAME, NANCY E	UNIVERSITY OF MICHIGAN AT ANN ARBOR
M01 RR000042	AGE AND MENOPAUSE EFFECTS ON INDICATORS OF BONE HEALTH	LUKACS, JANE L	UNIVERSITY OF MICHIGAN AT ANN ARBOR
M01 RR000046	WOMEN'S HEALTH INITIATIVE	HEISS, GERARDO	UNIVERSITY OF NORTH CAROLINA CHAPEL HILL
M01 RR000047	HORMONE REPLACEMENT THERAPY IN MENOPAUSAL WOMEN WITH EPILEPSY	HARDEN, CYNTHIA L.	WEILL MEDICAL COLLEGE OF CORNELL UNIV
M01 RR000048	EPIDEMIOLOGY OF OSTEOPOROSIS IN WOMEN WITH LUPUS - MAMDC PROJECT	RAMSEY-GOLDMAN, ROSALIND	NORTHWESTERN UNIVERSITY
M01 RR000051	DHEA, SEX STEROIDS AND COGNITION IN POST-MENOPAUSAL WOMEN	HIRSHMAN, ELLIOT	UNIVERSITY OF COLORADO HLTH SCIENCES CTR
M01 RR000051	INFLUENCE OF HORMONE REPLACEMENT THERAPY ON ARTERIAL FUNCTION/STRUCTURE	MOREAU, KERRIE	UNIVERSITY OF COLORADO HLTH SCIENCES CTR
M01 RR000051	MODULATION OF WHOLE BODY AND REGIONAL ADIPOSE TISSUE LIPOLYSIS AFTER MENOPAUSE	KOHRT, WENDY	UNIVERSITY OF COLORADO HLTH SCIENCES CTR
M01 RR000051	MECHANISMS OF VISCERAL FAT ACCUMULATION IN OLDER WOMEN	GOZANSKY, WENDEE	UNIVERSITY OF COLORADO HLTH SCIENCES CTR
M01 RR000051	MODULATION OF VISCERAL FAT BY ESTROGENS AFTER MENOPAUSE	KOHRT, WENDY	UNIVERSITY OF COLORADO HLTH SCIENCES CTR
M01 RR000052	EFFECT OF HORMONE REPLACEMENT ON THE PROGRESSION OF ATHEROSCLEROSIS...	OUYANG, PAMELA	JOHNS HOPKINS UNIVERSITY
M01 RR000054	SELECTIVE ESTROGEN RECEPTOR MODULATION: EFFECTS IN POST-MENOPAUSAL WOMEN	UDELSON, JAMES	NEW ENGLAND MEDICAL CENTER HOSPITALS
M01 RR000056	THE EFFECT OF PHYTOESTROGEN SUPPLEMENTATION ON POST-MENOPAUSAL ENDOMETRIUM	BALK, JUDY	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
M01 RR000056	CIRCULATING ANDROGENS LEVELS IN POSTMENOPAUSAL WOMEN W/POLYCYSTIC OVARY SYNDROME	KORYTKOWSKI, MARY	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
M01 RR000056	WOMEN'S HEALTH INITIATIVE	KULLER, LEWIS	UNIVERSITY OF PITTSBURGH AT PITTSBURGH

M01 RR000056	RANDOMIZED DBL-BLIND...HORMONE REPLACEMENT IN POSTMENOPAUSAL WOMEN W/SLE	MANZI, SUSAN	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
M01 RR000056	HORMONE METABOLISM AND BREAST MASSES	MODUGNO, FRANCESMARY	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
M01 RR000056	A FUNCTIONALLY BASED APPROACH TO THE TREATMENT OF INCONTINENCE	BORELLO-FRANCE, DIANE	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
M01 RR000058	CLINICAL TRIAL AND OBSERVATIONAL STUDY OF THE WOMEN'S HEALTH INITIATIVE	KOTCHEN, JANE	MEDICAL COLLEGE OF WISCONSIN
M01 RR000059	THE WOMEN'S HEALTH INITIATIVE	WALLACE, ROBERT B.	UNIVERSITY OF IOWA
M01 RR000065	PERIPHERAL VASCULAR ENDOTHELIAL FUNCTION AFTER MENOPAUSE	ARROWOOD, JAMES	VIRGINIA COMMONWEALTH UNIVERSITY
M01 RR000065	INSULIN RESISTANCE & CARDIOVASCULAR RISK IN POSTMENOPAUSAL WOMEN WITH PCOS	NESTLER, JOHN E	VIRGINIA COMMONWEALTH UNIVERSITY
M01 RR000065	PROGESTERONE ADMINISTRATION ON ENDOTHELIAL FUNCTION IN POSTMENOPAUSAL WOMEN	ARROWOOD, JAMES	VIRGINIA COMMONWEALTH UNIVERSITY
M01 RR000073	OVARIAN STEROIDS IN MENOPAUSAL WOMEN WITH ENDOMETRIAL CANCER	NAGAMANI, MANUBAI	UNIVERSITY OF TEXAS MEDICAL BR GALVESTON
M01 RR000073	EFFECT OF RALOXIFENE ON INSULIN SENSITIVITY IN NORMAL POSTMENOPAUSAL WOMEN	NAGAMANI, MANUBAI	UNIVERSITY OF TEXAS MEDICAL BR GALVESTON
M01 RR000080	SOY PHYTOESTROGEN AND CALCIUM SUPPLEMENTATION ON BONE RESORPTION/FORMATION	HARKNESS, LAURA	CASE WESTERN RESERVE UNIVERSITY
M01 RR000095	THE EFFECTS OF 3 DIFFERENT DOSES OF ENTERIC COATED BAYER ASPIRIN ON LEVELS OF	KERINS, DAVID	VANDERBILT UNIVERSITY
M01 RR000109	ESTROGEN MODULATION EFFECTS ON CHOLINERGIC FUNCTION IN POST-MENOPAUSAL WOMEN	NEWHOUSE, PAUL A	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE
M01 RR000109	EFFECT OF HRT ON CARDIOVASCULAR HEMODYNAMICS IN MENOPAUSAL WOMEN	SITES, CYNTHIA K	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE
M01 RR000109	MECHANISM OF MUSCLE PROTEIN LOSS IN MENOPAUSE	MATTHEWS, DWIGHT E	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE

M01 RR000109	ESTROGEN AND MOOD AND COGNITION FOLLOWING MONOAMINERGIC DEPLETION	NEWHOUSE, PAUL A	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE
M01 RR000109	ESTROGEN AND CHOLINERGIC FUNCTION IN NORMAL POST-MENOPAUSAL WOMEN	NEWHOUSE, PAUL A	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE
M01 RR000109	HORMONE REPLACEMENT THERAPY AND METABOLIC CARDIOVASCULAR RISK	SITES, CYNTHIA K	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE
M01 RR000109	ENERGY METABOLISM DURING THE MENOPAUSE TRANSITION	MATTHEWS, DWIGHT E	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE
M01 RR000109	HRT TO AUGMENT LOSS OF VISCERAL FAT AND IMPROVE INSULIN SENSITIVITY	MATTHEWS, DWIGHT E	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE
M01 RR000125	PERIMENOPAUSAL SYMPTOMS MANAGEMENT WITH ACUPUNCTURE	COHEN, SUSAN DSN	YALE UNIVERSITY
M01 RR000188	EFFECTS OF SOY ISOFLAVONES ON NITRIC OXIDE PRODUCTION IN POSTMENOPAUSAL WOMEN	WONG, WILLIAM	BAYLOR COLLEGE OF MEDICINE
M01 RR000334	STUDY OF TAMOXIFEN AND RALOXIFENE (STAR) FOR BREAST CANCER PREVENTION	NICHOLS, CRAIG	OREGON HEALTH & SCIENCE UNIVERSITY
M01 RR000334	BREAST CANCER SURVIVORS: EXERCISE AND RALOXIFENE	SCHWARTZ, ANNA	OREGON HEALTH & SCIENCE UNIVERSITY
M01 RR000400	SOY, PROBIOTICS, AND BREAST CANCER PREVENTION	KURZER, MINDY	UNIVERSITY OF MINNESOTA TWIN CITIES
M01 RR000425	CLINICAL TRIAL&OBSERVATIONAL STUDY OF WOMEN'S HEALTH INITIATIVE-WEST	CHLEBOWSKI, ROWAN T	HARBOR-UCLA RESEARCH & EDUC INST
M01 RR000585	SEROLOGIC SERBB1 IN HEALTHY WOMEN	BARON, ANDRE T	MAYO CLINIC ROCHESTER
M01 RR000585	BONE DENSITY AMONG HISPANIC OLMSTED COUNTY RESIDENTS: A CROSS-SECTIONAL AND LON	RIGGS, B LAWRENCE	MAYO CLINIC ROCHESTER
M01 RR000585	MECHANISM OF INCREASED OSTEOCLASTOGENESIS DURING ESTROGEN DEFICIENCY	EGHBALI, GUITI Z	MAYO CLINIC ROCHESTER
M01 RR000585	THE ROLE OF PARATHYROID HORMONE (PTH) IN AGE-RELATED CHANGES IN BONE TURNOVER	RIGGS, B LAWRENCE	MAYO CLINIC ROCHESTER
M01	SIMVASTIN/HRT IN POSTMENOPAUSAL WOMEN	GARG,	UNIVERSITY OF

RR000633	WITH NIDDM	ABHIMANYU	TEXAS SW MED CTR/DALLAS
M01 RR000645	THE FIBRINOLYTIC POTENTIAL OF ESTROGEN IN WOMEN	GIARDINA, ELSA-GRACE V	COLUMBIA UNIVERSITY HEALTH SCIENCES
M01 RR000645	RALOXIFENE IN PRIMARY HYPERPARATHYROIDISM	SILVERBERG, SHONNI J	COLUMBIA UNIVERSITY HEALTH SCIENCES
M01 RR000645	BLACK COHOSH AND HOT FLASHES	KRONENBERG, FREDI	COLUMBIA UNIVERSITY HEALTH SCIENCES
M01 RR000645	THE CHOICE PROJECT: COMPARING HEALTHY OPTIONS IN COOKING AND EATING	BILEZIKIAN, JOHN	COLUMBIA UNIVERSITY HEALTH SCIENCES
M01 RR000645	THE EFFECTS OF HORMONE REPLACEMENT THERAPY IN DIABETIC WOMEN	TUCK, CATHERINE	COLUMBIA UNIVERSITY HEALTH SCIENCES
M01 RR000645	ALZHEIMER'S DISEASE PREVENTION TRIAL WITH ESTROGEN	SANO, MARY	COLUMBIA UNIVERSITY HEALTH SCIENCES
M01 RR000827	GENDER DIFFERENCES IN SUSCEPTIBILITY TO FATTY ACID INDUCED INSULIN RESISTANCE	KRUSZYNSKA, YOLANTA	UNIVERSITY OF CALIFORNIA SAN DIEGO
M01 RR000827	HEALTH EFFECTS OF POSTMENOPAUSAL PHYTOESTROGEN USE	KRITZ-SILVERSTE, DONNA	UNIVERSITY OF CALIFORNIA SAN DIEGO
M01 RR000827	SOY AND POSTMENOPAUSAL HEALTH IN AGING (SOPHIA)	KRITZ-SILVERSTE, DONNA	UNIVERSITY OF CALIFORNIA SAN DIEGO
M01 RR000827	HORMONE REPLACEMENT THERAPY AND ADRENERGIC PHYSIOLOGY	MILLS, PAUL J	UNIVERSITY OF CALIFORNIA SAN DIEGO
M01 RR000833	MELATONIN TREATMENT FOR SLEEP DISTURBANCES DURING MENOPAUSE	DARKO, DENIS F	SCRIPPS RESEARCH INSTITUTE
M01 RR000847	SEX-STEROID CONTROL OF GH FEEDBACK ON EXERCISE	VELDHUIS, JOHANNES D	UNIVERSITY OF VIRGINIA CHARLOTTESVILLE
M01	EFFECTS OF AGE ON HYPOTHALAMIC-PITUITARY-OVARIAN ACTIVITY IN NORMAL	EVANS, WILLIAM S	UNIVERSITY OF VIRGINIA

RR000847	WOMEN		CHARLOTTESVILLE
M01 RR000865	PILOT PROJECT TO STUDY HRT, HPA AXIS REACTIVITY AND MEMORY FUNCTION	SEEMAN, TERESA	UNIVERSITY OF CALIFORNIA LOS ANGELES
M01 RR001032	THE ROLE OF ESTROGEN ON VASCULAR FUNCTION IN INSULIN RESISTANT WOMEN	GOLDFINE, ALLISON B	BETH ISRAEL DEACONESS MEDICAL CENTER
M01 RR001032	HORMONE REPLACEMENT IN MENOPAUSAL WOMEN WITH EPILEPSY	HERZOG, ANDREW G	BETH ISRAEL DEACONESS MEDICAL CENTER
M01 RR001066	RALOXIFENE ON BNE MASS & SERUM PROLACTIN LVLS/MENOPAUSAL WM W/HYPERPROLACTINEMIA	KLIBANSKI, ANNE	MASSACHUSETTS GENERAL HOSPITAL
M01 RR001066	PITUITARY CONTRIBUTION TO THE DECLINE IN GONADOTROPIN SECRETION WITH AGE	HALL, JANET E	MASSACHUSETTS GENERAL HOSPITAL
M01 RR001066	A GNRH ANTAGONIST (NAL-GLU GNRH ANTAGONIST) IN PMW	HALL, JANET E	MASSACHUSETTS GENERAL HOSPITAL
M01 RR001346	EFFECT OF JUMPING EXERCISE INTERVENTION BONE MINERAL DENSITY IN POST MENOP WMN	NEWSTEAD, ANN	UNIVERSITY OF TEXAS HLTH SCI CTR SAN ANT
M01 RR002558	BUCCAL ESTROGEN IN TOOTHPASTE STUDY	ALI, VASEEM	UNIVERSITY OF TEXAS HLTH SCI CTR HOUSTON
M01 RR002558	SAFETY OF ESTROGENS IN LUPUS ERYTHEMATOSUS - NATIONAL ASSESSMENT	FRIEDMAN, ALAN W	UNIVERSITY OF TEXAS HLTH SCI CTR HOUSTON
M01 RR002602	EFFECT OF PROGESTOGENS ON BONE AND COGNITION	MUSE, KEN	UNIVERSITY OF KENTUCKY
M01 RR002635	ADDITION OF TESTOSTERONE TO HRT ENHANCES QOL AND LIBIDO IN POSTMENOPAUSAL WOMEN	GINSBURG, ELIZABETH S	BRIGHAM AND WOMEN'S HOSPITAL
M01 RR002719	EFFECTS OF SEX HORMONE REPLACEMENT THERAPY ON COGNITION & MOOD IN OLDER ADULTS	MAKI, PAULINE	JOHNS HOPKINS UNIVERSITY
M01 RR002719	HORMONE REPLACEMENT THERAPY AFTER CORONARY ARTERY BYPASS SURGERY	OUYANG, PAMELA	JOHNS HOPKINS UNIVERSITY
M01 RR002719	ESTROGEN/SERMS EFFECTS ON COGNITION AND BRAIN FUNCTION	MAKI, PAULINE	JOHNS HOPKINS UNIVERSITY
M01 RR002719	WOMEN'S ANGIOGRAPHIC VITAMINS AND ESTROGEN (WAVE) TRIAL	OUYANG, PAMELA	JOHNS HOPKINS UNIVERSITY
M01	BLSA: PERIMENOPAUSAL INITIATIVE	BELLANTONI,	JOHNS HOPKINS

RR002719		MICHELE F	UNIVERSITY
M01 RR003186	WOMEN'S HEALTH INITIATIVE -- UNIVERSITY OF WISCONSIN-MADISON CLINICAL CENTER	ALLEN, CATHERINE I	UNIVERSITY OF WISCONSIN MADISON
M01 RR005096	EFFECTS OF ESTROGEN REPLACEMENT IN TYPE 2 DIABETES	FRIDAY, KAREN E.	TULANE UNIVERSITY OF LOUISIANA
M01 RR006192	EFFECT OF HORMONE REPLACEMENT THERAPY ON BONE IN OLDER WOMEN	PRESTWOOD, KAREN	UNIVERSITY OF CONNECTICUT SCH OF MED/DNT
M01 RR006192	TRANSDERMAL PROGESTERONE ON BONE TURNOVER	RAISZ, LAWRENCE G	UNIVERSITY OF CONNECTICUT SCH OF MED/DNT
M01 RR007122	KI-67 LEVELS IN BREAST CORE BIOPSY SPECIMENS FROM POSTMENOPAUSAL WOMEN	VITOLINS, MARA Z	WAKE FOREST UNIVERSITY HEALTH SCIENCES
M01 RR007122	WOMEN'S HEALTH INITIATIVE MEMORY STUDY (WHIMS)	VITOLINS, MARA Z	WAKE FOREST UNIVERSITY HEALTH SCIENCES
M01 RR007122	POSTMENOPAUSAL HORMONE REPLACEMENT THERAPY AFTER CORONARY BYPASS SURGERY (EAGER)	HERRINGTON, DAVID M	WAKE FOREST UNIVERSITY HEALTH SCIENCES
M01 RR007122	VASOMOTOR EFFECT OF HORMONAL REPLACEMENT REGIMENS	HUNDLEY, W GREGORY	WAKE FOREST UNIVERSITY HEALTH SCIENCES
M01 RR007122	WOMEN'S HEALTH INITIATIVE (WHI) VANGUARD CLINICAL CENTER TRIAL	BURKE, GREGORY L	WAKE FOREST UNIVERSITY HEALTH SCIENCES
M01 RR010284	ALZHEIMER—ESTROGEN	OBISESAN, THOMAS O	HOWARD UNIVERSITY
M01 RR010732	EFFECTS OF THE GLYCEMIC INDEX OF FOODS ON CVD RISK IN POST MENOPAUSAL WOMEN	PELKMAN, CHRISTINE L	PENNSYLVANIA STATE UNIV HERSHEY MED CTR
M01 RR010732	NUTRITIONAL STUDY IN POST MENOPAUSAL WOMEN	KRIS-ETHERTON, PENNY M	PENNSYLVANIA STATE UNIV HERSHEY MED CTR
M01 RR010732	EFFECTS OF THE GLYCEMIC INDEX OF FOODS ON CVD RISK IN POST-MENOPAUSAL WOMEN	PELKMAN, CHRISTINE L	PENNSYLVANIA STATE UNIV HERSHEY MED

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M01 RR013987	A PHASE I STUDY OF BLACK COHOSH AND RED CLOVER IN HEALTHY MENOPAUSAL WOMEN	SHULMAN, LEE PHILLIP	UNIVERSITY OF ILLINOIS AT CHICAGO
N02 RR001132	CLINICAL RESEARCH LRP	GOZANSKY, WENDOLYN S	UNIVERSITY OF COLORADO HEALTH SCI CTR
P20 RR015592	KY COBRE: ACTIONS OF ESTRADIOL & SERMS ON COGNITION, MOOD & EFFECT	KELLY, THOMAS	UNIVERSITY OF KENTUCKY
P41 RR000862	AMYLOIDOSIS IN RESPONSE TO OVARIECTOMY IN TRANSGENIC MODEL OF ALZHEIMERS DISEASE	DUFF, KAREN	ROCKEFELLER UNIVERSITY
P41 RR000954	WEIGHT LOSS & RESISTANCE TRAINING ON INSULIN ACTION IN POSTMENOPAUSAL WOMEN	JOSEPH, LYNDON JO	WASHINGTON UNIVERSITY
P41 RR000954	BONE DENSITY RESPONSE TO ESTROGEN REPLACEMENT IN ELDERLY WOMEN	VILLAREAL, DENNIS T	WASHINGTON UNIVERSITY
P41 RR001192	BREAST CANCER DETECTION USING FREQUENCY DOMAIN PHOTON MIGRATION	BUTLER, JOHN A	UNIVERSITY OF CALIFORNIA IRVINE
P41 RR011623	MECHANISMS OF RADIATION INDUCED OOCYTE LOSS	TILLY, JONATHAN Z	COLUMBIA UNIVERSITY HEALTH SCIENCES
P51 RR000163	OVARIAN STEROID REGULATION OF SEROTONIN NEURAL FUNCTION	BETHEA, CYNTHIA L	OREGON HEALTH & SCIENCE UNIVERSITY
P51 RR000163	COGNITION AND ESTROGEN IN MIDDLE-AGED FEMALE MONKEYS	VOYTKO, MARY	OREGON HEALTH & SCIENCE UNIVERSITY
P51 RR000165	EFFECTS OF ESTROGENS AND RALOXIFENE ON COGNITION IN AGED FEMALE RHESUS MONKEYS	LACREUSE, AGNES	EMORY UNIVERSITY
P51 RR000165	EFFECTS OF ESTROGENS ON COGNITION IN YOUNG FEMALE RHESUS	LACREUSE, AGNES	EMORY UNIVERSITY
P51 RR000169	COGNITIVE FUNCTION IN THE AGED MONKEY	RAPP, PETER R	UNIVERSITY OF CALIFORNIA DAVIS
P51 RR000169	TREATMENT OF OVARIECTOMIZED-INDUCED BONE LOSS IN CYNOMOLGUS MONKEYS	HENDRICKX, ANDREW G	UNIVERSITY OF CALIFORNIA DAVIS
P51 RR000169	ESTROGEN & AGING BRAIN	MORRISON, JOHN	UNIVERSITY OF CALIFORNIA DAVIS

P51 RR013986	ESTABLISHMENT OF AN OSTEOPENIC COLONY OF FEMALE BABOONS	CAREY, K DEE	SOUTHWEST FOUNDATION FOR BIOMEDICAL RES
P51 RR013986	A PILOT STUDY OF THE PHYSIOLOGY OF THE PERIMENOPAUSE IN BABOONS	HONORE, ERIKA K	SOUTHWEST FOUNDATION FOR BIOMEDICAL RES
P51 RR013986	A NONHUMAN PRIMATE MODEL OF NATURAL MENOPAUSE	HONORE, ERIKA K	SOUTHWEST FOUNDATION FOR BIOMEDICAL RES
R01 RR014099	NEW TECHNIQUES IN DIAGNOSING OSTEOARTHRITIS: MENOPAUSE	CARLSON, CATHY SUE	UNIVERSITY OF MINNESOTA TWIN CITIES
R24 RR016535	THE YUCATAN MICROPIG CARDIOVASCULAR MODEL OF MENOPAUSE: SOY DIET	GOODRICH, JAMES A	MEDICAL UNIVERSITY OF SOUTH CAROLINA

GRANT NUMBER	TITLE	PRINCIPAL INVESTIGATOR
G12RR003051	ACT 5 III: WOMEN HEALTH: MENOPAUSE & HEALTH IN HISPANIC WOMEN IN PUERTO RICO	ROMAGUERA, JOSEFINA
G12RR013646	P2: ESTROGEN REPLACEMENT THERAPY & NEURON STRUCTURE: ALZHEIMERS	CLAIBORNE, BRENDA J
K01RR000170	NON HUMAN PRIMATE MODEL OF NATURAL MENOPAUSE CARDIOVASCULAR DIS OSTEOPOROSIS	HONORE, ERIKA K
K23RR016067	WOMEN AT HIGH RISK FOR CAD AFTER MENOPAUSE: BENEFITS OF ERT	CARR, MOLLY C
K23RR016321	POSTMENOPAUSAL HORMONAL REPLACEMENT THERAPY SYMPATHIC NERVE & HYPERTESION	VONGPATANASIN, WANPEN
K23RR017043	NEUROBIOLOGICAL EFFECT OF LONG-TERM ESTROGEN REPLACEMENT	SMITH, YOLANDA R
M01RR000030	HEART DISEASE IN WOMEN: ESTROGEN EFFECTS ON HEMODYNAMICS	SHERWOOD, ANDREW
M01RR000032	POST MENOPAUSAL HORMONE THERAPY	GOWER, BARBARA
M01RR000034	IMPACT OF ENZYME-INDUCING ANTIEPILEPTIC DRUGS ON HORMONE REPLACEMENT THERAPY	MCAULEY, JAMES W
M01RR000036	WASHINGTON UNIVERSITY CLAUDE D. PEPPER OAIC.	HOLLOSZY, JOHN
M01RR000037	FOLLICLE DEVELOPMENT STUDY	KLEIN, NANCY
M01RR000037	ESTROGENS, BODY FAT AND DYSLIPIDEMIA AT MENOPAUSE	CARR, MOLLY
M01RR000037	SLEEP IN OLDER WOMEN: EFFECTS OF ESTROGEN	MOE, KAREN
M01RR000037	EXERCISE EFFECTS ON HORMONES IN POST-MENOPAUSAL WOMEN	MCTIERNAN, ANNE
M01RR000040	THE EFFECTS OF ESTROGEN AND DHEA SUPPLEMENTATION ON SERUM LIPIDS, & MUSCLE MASS	BARNHART, KURT
M01RR000040	NMR IMAGING AND STEROLOGIC ANALYSIS OF TRABECULAR BONE	WEHRLI, FELIX
M01RR000042	ROLE OF GLUCOSE IN MENOPAUSAL HOT FLASHES	DORMIRE, SHARON L
M01RR000042	SAFETY OF ESTROGENS IN LUPUS ERYTHEMATOSUS NATIONAL ASSESSMENT (SELENA)	MCCUNE, WILLIAM J
M01RR000042	EFFECT OF TRANSDERMAL ESTROGEN & ORAL ISOFLAVONE ON SEX HORMONE-BINDING GLOBULIN	LEE, CATHY C
M01RR000042	THE ROLE OF HYPOTHALAMIC AGING IN MENOPAUSE	REAME, NANCY E
M01RR000042	AGE AND MENOPAUSE EFFECTS ON INDICATORS OF BONE HEALTH	LUKACS, JANE L
M01RR000046	WOMEN'S HEALTH INITIATIVE	HEISS, GERARDO
M01RR000047	HORMONE REPLACEMENT THERAPY IN MENOPAUSAL WOMEN WITH EPILEPSY	HARDEN, CYNTHIA L.
M01RR000048	EPIDEMIOLOGY OF OSTEOPOROSIS IN WOMEN WITH LUPUS - MAMDC PROJECT	RAMSEY-GOLDMAN, ROSALIND
M01RR000051	DHEA, SEX STEROIDS AND COGNITION IN POST-MENOPAUSAL WOMEN	HIRSHMAN, ELLIOT
M01RR000051	INFLUENCE OF HORMONE REPLACEMENT THERAPY ON ARTERIAL FUNCTION/STRUCTURE	MOREAU, KERRIE
M01RR000051	MODULATION OF WHOLE BODY AND REGIONAL ADIPOSE TISSUE LIPOLYSIS AFTER MENOPAUSE	KOHRT, WENDY
M01RR000051	MECHANISMS OF VISCERAL FAT ACCUMULATION IN OLDER WOMEN	GOZANSKY, WENDEE
M01RR000051	MODULATION OF VISCERAL FAT BY ESTROGENS AFTER MENOPAUSE	KOHRT, WENDY

M01RR000052	EFFECT OF HORMONE REPLACEMENT ON THE PROGRESSION OF ATHEROSCLEROSIS...	OUYANG, PAMELA
M01RR000054	SELECTIVE ESTROGEN RECEPTOR MODULATION: EFFECTS IN POST-MENOPAUSAL WOMEN	UDELSON, JAMES
M01RR000056	THE EFFECT OF PHYTOESTROGEN SUPPLEMENTATION ON POST-MENOPAUSAL ENDOMETRIUM	BALK, JUDY
M01RR000056	CIRCULATING ANDROGENS LEVELS IN POSTMENOPAUSAL WOMEN W/POLYCYSTIC OVARY SYNDROME	KORYTKOWSKI, MARY
M01RR000056	WOMEN'S HEALTH INITIATIVE	KULLER, LEWIS
M01RR000056	RANDOMIZED DBL-BLIND...HORMONE REPLACEMENT IN POSTMENOPAUSAL WOMEN W/SLE	MANZI, SUSAN
M01RR000056	HORMONE METABOLISM AND BREAST MASSES	MODUGNO, FRANCESMARY
M01RR000056	A FUNCTIONALLY BASED APPROACH TO THE TREATMENT OF INCONTINENCE	BORELLO-FRANCE, DIANE
M01RR000058	CLINICAL TRIAL AND OBSERVATIONAL STUDY OF THE WOMEN'S HEALTH INITIATIVE	KOTCHEN, JANE
M01RR000059	THE WOMEN'S HEALTH INITIATIVE	WALLACE, ROBERT B.
M01RR000065	PERIPHERAL VASCULAR ENDOTHELIAL FUNCTION AFTER MENOPAUSE	ARROWOOD, JAMES
M01RR000065	INSULIN RESISTANCE & CARDIOVASCULAR RISK IN POSTMENOPAUSAL WOMEN WITH PCOS	NESTLER, JOHN E
M01RR000065	PROGESTERONE ADMINISTRATION ON ENDOTHELIAL FUNCTION IN POSTMENOPAUSAL WOMEN	ARROWOOD, JAMES
M01RR000073	OVARIAN STEROIDS IN MENOPAUSAL WOMEN WITH ENDOMETRIAL CANCER	NAGAMANI, MANUBAI
M01RR000073	EFFECT OF RALOXIFENE ON INSULIN SENSITIVITY IN NORMAL POSTMENOPAUSAL WOMEN	NAGAMANI, MANUBAI
M01RR000080	SOY PHYTOESTROGEN AND CALCIUM SUPPLEMENTATION ON BONE RESORPTION/FORMATION	HARKNESS, LAURA
M01RR000095	THE EFFECTS OF 3 DIFFERENT DOSES OF ENTERIC COATED BAYER ASPIRIN ON LEVELS OF	KERINS, DAVID
M01RR000109	ESTROGEN MODULATION EFFECTS ON CHOLINERGIC FUNCTION IN POST-MENOPAUSAL WOMEN	NEWHOUSE, PAUL A
M01RR000109	EFFECT OF HRT ON CARDIOVASCULAR HEMODYNAMICS IN MENOPAUSAL WOMEN	SITES, CYNTHIA K
M01RR000109	MECHANISM OF MUSCLE PROTEIN LOSS IN MENOPAUSE	MATTHEWS, DWIGHT E
M01RR000109	ESTROGEN AND MOOD AND COGNITION FOLLOWING MONOAMINERGIC DEPLETION	NEWHOUSE, PAUL A
M01RR000109	ESTROGEN AND CHOLINERGIC FUNCTION IN NORMAL POST-MENOPAUSAL WOMEN	NEWHOUSE, PAUL A
M01RR000109	HORMONE REPLACEMENT THERAPY AND METABOLIC CARDIOVASCULAR RISK	SITES, CYNTHIA K
M01RR000109	ENERGY METABOLISM DURING THE MENOPAUSE TRANSITION	MATTHEWS, DWIGHT E
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M01RR000125	PERIMENOPAUSAL SYMPTOMS MANAGEMENT WITH ACUPUNCTURE	COHEN, SUSAN DSN
M01RR000188	EFFECTS OF SOY ISOFLAVONES ON NITRIC OXIDE PRODUCTION IN POSTMENOPAUSAL WOMEN	WONG, WILLIAM

M01RR000334	STUDY OF TAMOXIFEN AND RALOXIFENE (STAR) FOR BREAST CANCER PREVENTION	NICHOLS, CRAIG
M01RR000334	BREAST CANCER SURVIVORS: EXERCISE AND RALOXIFENE	SCHWARTZ, ANNA
M01RR000400	SOY, PROBIOTICS, AND BREAST CANCER PREVENTION	KURZER, MINDY
M01RR000425	CLINICAL TRIAL&OBSERVATIONAL STUDY OF WOMEN'S HEALTH INITIATIVE-WEST	CHLEBOWSKI, ROWAN T
M01RR000585	SEROLOGIC SERBB1 IN HEALTHY WOMEN	BARON, ANDRE T
M01RR000585	BONE DENSITY AMONG HISPANIC OLMSTED COUNTY RESIDENTS: A CROSS-SECTIONAL AND LON	RIGGS, B LAWRENCE
M01RR000585	MECHANISM OF INCREASED OSTEOCLASTOGENESIS DURING ESTROGEN DEFICIENCY	EGHBALI, GUITI Z
M01RR000585	THE ROLE OF PARATHYROID HORMONE (PTH) IN AGE-RELATED CHANGES IN BONE TURNOVER	RIGGS, B LAWRENCE
M01RR000633	SIMVASTIN/HRT IN POSTMENOPAUSAL WOMEN WITH NIDDM	GARG, ABHIMANYU
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M01RR000645	RALOXIFENE IN PRIMARY HYPERPARATHYROIDISM	SILVERBERG, SHONNI J
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M01RR000645	THE EFFECTS OF HORMONE REPLACEMENT THERAPY IN DIABETIC WOMEN	TUCK, CATHERINE
M01RR000645	ALZHEIMER'S DISEASE PREVENTION TRIAL WITH ESTROGEN	SANO, MARY
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M01RR000827	HEALTH EFFECTS OF POSTMENOPAUSAL PHYTOESTROGEN USE	KRITZ-SILVERSTE, DONNA
M01RR000827	SOY AND POSTMENOPAUSAL HEALTH IN AGING (SOPHIA)	KRITZ-SILVERSTE, DONNA
M01RR000827	HORMONE REPLACEMENT THERAPY AND ADRENERGIC PHYSIOLOGY	MILLS, PAUL J
M01RR000833	MELATONIN TREATMENT FOR SLEEP DISTURBANCES DURING MENOPAUSE	DARKO, DENIS F
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M01RR000847	EFFECTS OF AGE ON HYPOTHALAMIC-PITUITARY-OVARIAN ACTIVITY IN NORMAL WOMEN	EVANS, WILLIAM S
M01RR000865	PILOT PROJECT TO STUDY HRT, HPA AXIS REACTIVITY AND MEMORY FUNCTION	SEEMAN, TERESA
M01RR001032	THE ROLE OF ESTROGEN ON VASCULAR FUNCTION IN INSULIN RESISTANT WOMEN	GOLDFINE, ALLISON B
M01RR001032	HORMONE REPLACEMENT IN MENOPAUSAL WOMEN WITH EPILEPSY	HERZOG, ANDREW G
M01RR001066	RALOXIFENE ON BNE MASS & SERUM PROLACTIN LVLS/MENOPAUSAL WM W/HYPERPROLACTINEMIA	KLIBANSKI, ANNE
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M01RR002719	HORMONE REPLACEMENT THERAPY AFTER CORONARY ARTERY BYPASS SURGERY	OUYANG, PAMELA
M01RR002719	ESTROGEN/SERMS EFFECTS ON COGNITION AND BRAIN FUNCTION	MAKI, PAULINE
M01RR002719	WOMEN'S ANGIOGRAPHIC VITAMINS AND ESTROGEN (WAVE) TRIAL	OUYANG, PAMELA
M01RR002719	BLSA: PERIMENOPAUSAL INITIATIVE	BELLANTONI, MICHELE F
M01RR003186	WOMEN'S HEALTH INITIATIVE -- UNIVERSITY OF WISCONSIN-MADISON CLINICAL CENTER	ALLEN, CATHERINE I
M01RR005096	EFFECTS OF ESTROGEN REPLACEMENT IN TYPE 2 DIABETES	FRIDAY, KAREN E.
M01RR006192	EFFECT OF HORMONE REPLACEMENT THERAPY ON BONE IN OLDER WOMEN	PRESTWOOD, KAREN
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M01RR007122	WOMEN'S HEALTH INITIATIVE MEMORY STUDY (WHIMS)	VITOLINS, MARA Z
M01RR007122	POSTMENOPAUSAL HORMONE REPLACEMENT THERAPY AFTER CORONARY BYPASS SURGERY (EAGER)	HERRINGTON, DAVID M
M01RR007122	VASOMOTOR EFFECT OF HORMONAL REPLACEMENT REGIMENS	HUNDLEY, W GREGORY
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M01RR010284	ALZHEIMER—ESTROGEN	OBISESAN, THOMAS O
M01RR010732	EFFECTS OF THE GLYCEMIC INDEX OF FOODS ON CVD RISK IN POST MENOPAUSAL WOMEN	PELKMAN, CHRISTINE L
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M01RR010732	EFFECTS OF THE GLYCEMIC INDEX OF FOODS ON CVD RISK IN POST-MENOPAUSAL WOMEN	PELKMAN, CHRISTINE L
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