A Working Document

NIH Research And Other Efforts Related To The Menopausal Transition

(Revised November 2003)

The Office of Research on Women's Health

and the

Coordinating Committee on Research on Women's Health

National Institutes of Health

Report Compiled by:

Vivian W. Pinn, M.D., Director
Office of Research on Women's Health

Angela Bates, Program Analyst
Office of Research on Women's Health

TABLE OF CONTENTS

INTRODUCTION

COORDINATING COMMITTEE FOR RESEARCH ON WOMEN'S HEALTH ROSTER

WORKING DEFITIONS OF MENOPAUSE

WEB RESOURCES ON MENOPAUSE HORMONE THERAPY

MENOPAUSE RELATED RESEARCH

National Cancer Institute (NCI)……1
National Eye Institute (NEI) ……22
National Heart, Lung and Blood Institute (NHLBI) ……31
National Institute on Aging (NIA) …… 37
National Institute on Alcohol Abuse and Alcoholism (NIAAA) ……..49
National Institute of Allergy and Infectious Diseases (NIAID) ……... 52
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) ……... 56
National Institute of Child Health and Human Development (NICHD) …….. 71
National Institute on Deafness and Other Communication Disorders (NIDCD) ……. 76
National Institute of Dental and Craniofacial Research (NIDCR) ……... 78
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) …… 81
National Institute on Drug Abuse (NIDA) ……89
National Institute of Environmental Health Sciences (NIEHS) ……... 91
National Institute of Mental Health (NIMH) …… 93
National Institute of Neurological Disorders and Stroke (NINDS) …… 101
National Institute of Nursing Research (NINR) ……... 106
National Center for Complementary and Alternative Medicine (NCCAM) …… 112
National Center for Research Resources (NCRR) ……115
National Center for Minority Health and Health Disparities (NCMHD) ……. 125

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[a]. 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[b] (HT), and there were about 17.5 million women total taking HT to combat the biological effects of menopause[c]. 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, 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

[a] North American Menopause Society, http://www.menopause.org/aboutmeno/sga.pdf
[b] "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.
[c] "Study: Hormones Don't Protect Women From Heart Disease." Okie, S.Washington Post. July 24, 2001.

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 Institute of General Medical Sciences (NIGMS), National Human Genome Research Institute (NHGRI), Fogarty International Center (FIC), National Institute of Biomedical Imaging and Bioengineering (NIBIB), Center for Scientific Review and the National Library of Medicine (NLM).

2003 COORDINATING COMMITTEE ON RESEARCH ON WOMEN'S HEALTH

Vivian W. Pinn, Chair ORWH Joyce Rudick, Exec. Sec. ORWH

IC	Representative	Alternate
NIDA	Cora Lee Wetherington	Adele Roman
NICHD	Judith Whalen	Estella Parrott
NHLBI	Barbara Liu	Cindy Palace
NCRR	Susan Kayar	Sheila McClure
NIAMS	Julia Freeman	Charisse Lamar
NLM	Valerie Florance	
NIGMS	Pamela Marino	Ann Hagan
NIEHS	Anne Sassaman	Sheila Newton
NCI	Anna Levy	Cheri Nichols
NIA	Marta Campbell	Barbara Kellner
NINR	Janice Phillips	Yvonne Bryan
NINDS	Patricia Turner	Brandy Fureman
NHGRI	Karen DeLeon	Laura Rodriguez
NEI	Ellen S. Liberman	Natalie Kurinijj
NIDCR	Maria Canto	Ruth Nowjack-Raymer
NIDCD	Lana Shekim	Amy Donahue
NIAID	Angela Magliozzi	Milton Hernandez
NIDDK	Eleanor Hoff	Mary Hanlon
NIMH	Mary Blehar	Ernest Marquez
NIAAA		Diedra Roach
FIC	Karen Hofman	Sharon Hrynkow
CSR	Denise Wiesch	Elaine Sierra-Rivera
NIBIB	Donna Dean	Joan Harmon
CC	Deborah Dozier-Hall	Walter Jones
NCCAM	Heather Miller	
NCMHD	John Ruffin	Jean Flag-Newton
OAR		Susan Wise
OSE	Bonnie Kalberer	
OCL	Tom Gallagher	Walter Mitten
OC	John Burklow	
OBSSR	Virginia Cain	Susan Solomon
ODS	Mary Francis Picciano	
OE	Brenda Hanning	James Alexander
OSP	Cheryl McDonald	Lana Skirboll
OIR	Esther Sternberg	Barbara Vonderhaar
OLPA	Anne Houser	
OEODM	Joan Brogan	O. Marcella Haynes
OER		Belinda Seto

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

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*

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

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)*

Additionally, 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.

NCI Menopause Related Grants

(Includes projects funded through September 30, 2002, but not may not include all projects funded through July 30, 2003)
*(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	2004	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.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
CA18119	Katzenellenbogen, Benita	2004	University of Illinois Urbana-Champaign	Antiestrogens--Mechanism of Antagonist Action	Breast Cancer-Related Biology	Antiestrogens (AEs) are the most widely used agents for the treatment of hormone-responsive breast cancer, and the AE tamoxifen has also proven to be effective in preventing breast cancer. AEs are also unique ligands useful for understanding the tissue selective actions of certain estrogens, an important issue in menopausal hormone replacement therapy, and for probing the intriguing pharmacology of the two estrogen receptor (ER) subtypes, ERalpha and ERbeta, and their roles in breast cancer and other estrogen target cells. In this application, we are proposing to investigate two new aspects of the action of AEs. The first aspect deals with the ability of certain proteins (denoted PAAs for "Potentiators of Antiestrogen Activity") that we have identified recently, to enhance the potency of AEs as inhibitors of estrogens. The levels and activity of these small, estrogen receptor-selective proteins could account for the differential tissue selectivity of AEs and for the ability of ER-containing breast tumors to be either highly sensitive, or resistant to AE therapy. We propose to identify and characterize PAAs, by examining their roles as modulators of AE action in target cells and eterminants of hormonal resistance in breast cancer, by elucidating their interaction domains with ER, their subcellular distribution, and their interaction with other ER coregulators, and by performing structural analyses on PAA-ER complexes. The second aspect also derives from our recent work in which we have found that certain antioxidant/cytoprotective genes are upregulated by AEs and inhibited by estrogens. We propose to identify and analyze the regulation of genes selectively upregulated by AEs, by searching for other genes that are AE stimulated and estrogen suppressed, by analyzing the gene regulatory regions mediating the selective activation by AEs, by determining the ERalpha and ERbeta selectivity of this regulation, and by examining whether other antioxidant genes involved in cytoprotection against reactive oxygen species are upregulated by AEs. The studies we propose should provide significant new insight into how AEs act, what cellular factors determine their effectiveness and tissue selectivity, and how their gene regulating activities contribute to their beneficial antiproliferative, tumor suppressive, and cytoprotective actions in breast cancer treatment and prevention.
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	2002	Michigan State University	Stroma and Mammary Gland Cell Proliferation	Breast Cancer-related Biology	Regulation of mammary gland development at puberty and the cyclical changes that occur in the adult mammary gland during pregnancy and lactation are highly dependent upon estrogen (E) and progesterone (P). During normal development the mammary gland undergoes reversible changes from hormone responsive to hormone refractory states. It is the long- term goal of this proposal to determine how these changes in responsiveness to E and P occur. Mammary stroma plays a critical role in mediating and inducing the proliferative effects of E and P in the mammary epithelium in vivo. The hypothesis being tested in this proposal is that the mitogenic effects of E and P are mediated by stroma-derived growth factors and extracellular matrix (ECM) molecules. We have developed a novel primary co-culture system of mammary epithelial cells and mammary stromal cells in serum-free medium in which the epithelial cells exhibit a proliferative response to both e and P. Using this culture system we will: 1) Identify the respective roles of mammary adipocytes and fibroblasts and characterize the nature of their interactions with epithelial cells; 2) Determine the role of growth factors, EGF, IGF-I, HGF, IGF binding proteins and their respective receptors (EGF-R, IGF-R and c-met) in E and P responsiveness in vitro and in vivo; 3) Define the role of stroma-derived ECM proteins (collagen IV, fibronectin and laminin) and their integrins in mediating E and P responsiveness; 4) Determine if estrogen responsiveness is determined by receptor (ER) isoform (alpha or beta) expression in epithelial and stromal cells. In order to understand E action in the stroma vs. epithelium, the temporal and cellular distribution of ER isoforms will be analyzed in relation to E responsiveness, both in vivo and in vitro. Determining the mechanisms that mediate epithelial-stromal cell interactions in normal mammary gland development and epithelial cell proliferation may provide a conceptual basis for novel approaches that focus on mammary stromal as a potential target for human breast cancer prevention and treatment.

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	We propose to continue to evaluate subcategories of benign breast disease in relation to risk of breast cancer. In addition, interactions between these characteristics and established and hypothesized risk factors for breast cancer will be examined using prospectively collected data. In particular, we will examine interactions between atypical hyperplasia and family history of breast cancer, menopause, use of postmenopausal estrogens, past use of oral contraceptives and relative weight (weight/height2), alcohol intake, dietary fat, intake of vitamin A (preformed and carotene), vitamin E, and caffeine. The proposed study is nested case-control within the Nurses' Health Study, a cohort of 121,700 US female registered nurses, currently aged 444-69 who were enrolled in a prospective study of risk factors for breast cancer in 1976 and who have been followed with biennial questionnaires since then. In addition, we add 50 cases and their controls from the Nurses' Health Study II. An extensively validated semi-quantitative food frequency questionnaire administered in 1980 enables us to assess the dietary variables. We propose to obtain and review histopathology slides from an additional 500 women with breast cancer diagnosed between return of the 1988 NHS questionnaire and the 1996 questionnaire who have a history of an earlier biopsy for benign breast disease and 2218 controls randomly selected from among women with a history of biopsy for benign breast disease in the cohort. Slides will be independently reviewed in a blinded fashion by two pathologists and graded according to the classification system based on that of Dr.Page. An histopathologic aim is to define objective criteria for the architecture and morphology of atypical hyperplasia. The relative risk of breast cancer associated with subcategories of benign breast disease (nonproliferative, proliferative, atypical) will be calculated using the women with no history of benign breast disease in the Nurses' Health Study cohort as a reference group. Potential interactions with epidemiologic and dietary risk factors will be assessed by stratified and multivariate analysis. We will also analyze data from the Nurses' Health Study II to examine the relation between long term use of oral contraceptives before first pregnancy and risk of atypical hyperplasia on breast biopsy.
CA49449	Hankinson, Susan	2004	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	We propose to analyze blood samples in a "nested" case-control manner from the 32,825 participants in the Nurses' Health Study (NHS) who provided samples in 1989-1990 and were 43 to 69 years of age at that time. The samples have been stored at less than or equal to 130 degrees C, in liquid nitrogen freezers, since collection. Laboratory analyses will be conducted on plasma samples from women who developed disease after donating a blood sample and matched controls who remained disease-free, thus efficiently utilizing these prospectively collected samples. We will concentrate on several major hypotheses, i.e., hormonal and nutritional determinants of disease risk. Specifically, we will examine (1) endogenous hormone levels (estradiol [both free and bound fractions], estrone, androgens, progesterone and prolactin) in relation to breast cancer risk in postmenopausal women, (2) antioxidant levels in relation to risk of breast cancer, (3) levels of folate, iron, fatty acids, antioxidants and vitamin D in relation to both colon cancer and colon polyps, and (4) levels of lipids, fatty acids, homocysteine, folate, ferritin and antioxidants in relation to risk of myocardial infarction and stroke. Most of the nutrients we propose to examine are hypothesized to influence development of both cancer and cardiovascular disease, thus the analyses will provide a better understanding of the influence of these factors on overall disease risk. The ongoing NHS will provide follow-up and documentation of cancers (CA 40356) and cardiovascular outcomes (HL 34594) in addition to information on important covariates (such as exogenous hormone use, other dietary factors, smoking status, and body mass index, among others) for the proposed study. Participation in the NHS has been high: of the 121,700 women, approximately 90% continue to respond to the questionnaires, and vital status has been documented for >98%. Overall, the large size of the cohort, the prospective design, the high follow-up rate, the detailed exposure data, and the availability of archived blood specimens provide 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	2004	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	An ongoing 17 year follow-up study of 120,000 U.S. nurses has produced important information on causes and preventives of cancer and cardiovascular disease in white women (some 100 papers to date), and other large follow-up studies of white women have been started more recently. There are no comparable studies in black women, who bear a greater burden of illness and mortality. [Results on the etiology of disease in white women may not be generalizable to black women because of genetic differences, differences in risk factors, or other reasons.] We propose to conduct a large prospective follow-up study of black women to provide informative data on risk factors for cancer, cardiovascular disease, and other major illnesses, with an emphasis on the health effects of obesity. Other factors to be assessed include cigarette smoking, physical activity, alcohol use, die, exogenous estrogen use, and reproductive factors. We will enroll, by means of a mailed questionnaire, 50,000 black women up to age 69 years who are members of the National Education Association, employees of the federal government, nurses, or friends of these women. These women were chosen because of evidence that they can provide reliable health information and be followed with few losses. Pilot studies carried out with the assistance of both the National Education Association and the U.S. Office of Personnel Management have demonstrated the feasibility of the project. An Advisory Board of black women knowledgeable about health problems in the black community has participated and will continue to give advice and guidance; expert consultants on black women's health will have important input to the study. The initial questionnaire will collect information on exposures and covariates of interest. Follow-up mail questionnaires at 2-year intervals will update information and ascertain incident cases of cancer, cardiovascular disease, and other major illnesses; diagnoses will be documented by review of medical records and other documents. Deaths will be ascertained from families and friends and through the National Death Index. Interim mailings will be made to sustain the interest of the participants and to inform them of study results. This study will provide needed information on the etiology of disease in black women, a heretofore neglected group in health studies. [The etiologic results will generally be applicable to millions of U.S. black women, including poor women,] and the results will be useful in preventive programs focused on reducing morbidity and mortality.
CA60050	Shapiro, Charles	1998	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 e 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	Taplin, Stephen	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.
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.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
CA72787	Daling, Janet	2002	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.
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.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
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	2003	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.
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.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
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.
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.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
CA77596	Strom, Brian	2002	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.
CA77617	Sessions, 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.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
CA77708	Greendale, Gail	2002	University of California Los Angeles	Sex Steroids and Mammogram Density in the Postmenopause	Breast Endogenous Factors in the origin and cause of cancer	Epidemiologic studies find that increased 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 focuses on 3 major questions: 1) are endogenous levels of sex steroids in postmenopausal women related to mammographic density; 2) does treatment with postmenopausal estrogen and estrogen/progestin therapy increase mammographic density; and 3) do the serum levels of estrone achieved as a result of treatment with postmenopausal hormone therapy predict change in mammographic density? To address these questions, the amount of density of mammograms performed during the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial will be determined using a computer-based threshold technique. PEPI was a 3-year, randomized placebo controlled trial of conjugated equine estrogens (CEE) vs. CEE plus one of 3 progestin regimens, which enrolled 875 postmenopausal women aged 45-64 at baseline. Data already collected as part of PEPI that will be used in this project will include: endogenous sex steroids at baseline, PEPI treatment assignment, estrone serum levels on-treatment, and necessary covariates. The project will last 3 years and take place at 3 sites: UCLA, USC, and Bowman Gray. The specific aims are to: 1) measure the density of mammograms performed at baseline and 12 months; 2) determine whether baseline mammographic density is associated with endogenous levels of sex steroids; 3) quantify the relation between change in mammographic density and adherence to treatments; and 4) determine whether changes density are associated with serum levels of estrone achieved as a result of hormone therapy. By assessing density changes in mammograms with this computer-based method, which has been previously linked to a quantified increase in risk of breast cancer, it may be possible to assess how much of a risk-increase would be predicted by hormone use. The investigators state that this may serve as the first in a series of investigations that would allow identification of those women at higher risk of developing breast toxicity from postmenopausal supplemental hormone use.
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	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.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
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.
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/I/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.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
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.
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.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
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.
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?

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
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.
CA89552	Habel, Leslie	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.

Grant #	Principal Investigator	Last Year Active	Institution	Project Title	Cancer Site/ Area of Research	Abstract
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
CA90440-02002	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.
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.

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.
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	Lacey, James	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	Schwartz, Anna	2004	Oregon Health Science University	Breast Cancer Survivors: Exercise and Raloxifene	Breast Behavior related to Cancer Control	It is estimated that 178,799 women will be diagnosed with breast cancer in 1998. While breast cancer has become more treatable, the long-term treatment-related side effects have a significant negative effect on morbidity and non-cancer related risk of mortality. The increasingly common use of adjuvant chemotherapy for breast cancer has led to a rise in long-term treatment- related side effects including osteoporosis, early menopause, increased risk for cardiovascular disease, and declines in quality of life. Osteoporosis is a major public health problem and a common finding in breast cancer survivors. Nationally, 20 million women are estimated to be at risk for osteoporosis, with 1.3 million sustaining osteoporotic fractures. Four factors place breast cancer survivors at high risk for muscle, bone and cardiovascular complications: inactivity, menopause (especially premature menopause), chemotherapy and catabolic steroids. This innovative study will use a randomized placebo-controlled design to test the effects of (a) exercise and (b) raloxifene in postmenopausal breast cancer survivors (N=240) between 3 months and one year after completing chemotherapy on: one resorption, formation and density (serum osteocalcin and bone specific AST, urine n-telopeptide, DEXA scan); multidimensional quality of life (SF-36, 12-minute walk, muscle strength, fatigue, menopausal vasomotor symptoms positive and negative affect, and Trail Making); and lipid profile (serum lipid levels). Subjects in the exercise intervention will follow a supervised home-based exercise program and asked to exercise 5 days/week. Exercise dose and adherence will be monitored with Caltrac accelerometers, exercise logs, regularly scheduled follow-up phone calls and supervised exercise sessions, and results on 12-minute walks and 1-repetition maximum tests. Subjects in the ralosifene and placebo control groups will be asked to take the medication (60mg/day) or placebo as prescribed. Subjects in the exercise+raloxifene group will be asked to take the medication and follow the exercise program. All subjects will be instructed to take a daily calcium supplement (1000mg/day). Subjects will be followed for 2 years. All measures will be re-evaluated at 3-month intervals except the DEXA scans, which will be obtained at 12-month intervals. Results of this study may reduce the morbidity, mortality and health care costs of these common, long- term complications that confront breast cancer survivors.

NATIONAL EYE INSTITUTE

(NEI)

NEI Menopause Related Research Active Research FY2003			
Grant No.	**Title**	***Principle Investigator***	**Site**
R01EY011239	Aquarporin Water Channel Proteins in Eye	Agre, Peter C, MD	Johns Hopkins University, Baltimore, Md
U10EY013626	Incidence of late macular degeneration in older women	Coleman, Anne L, Ph.D	University Of California Los Angeles,
5R01EY006177-19	Mechanism of Lacrimal Gland Secretion	Dartt, Darlene A, Ph.D	Schepens Eye Research Institute, Boston, Ma
R01EY014594	Female Hormones and Vision	Eisner, Alvin, Ph.D	Oregon Health & Science University, Portland, Or
R01EY014477	ECM Regulation by Estrogen in ARMD	Elliot, Sharon, Ph.D	University Of Miami, Coral Gables, Fl
R01EY003306	Mucins Of The Ocular Surface	Gipson, Ilene K., Ph.D	Schepens Eye Research Institute, Boston, Ma
R01EY011224	Proteins In Molecular Mechanisms Of Tear Film Formation	Glasgow, Ben J, MD	University Of California Los Angeles
R01EY011386	Microtubule-Based Transport In Lacrimal Gland Function	Hamm-Alvarez, Sarah F, BA	University Of Southern California
R01EY009611	Prospective Study Of Risk Factors For Eye Disease	Hankinson, Susan E	Brigham And Women's Hospital, Boston, MA
R03EY014021	Capillary Electrophoresis Profiling of Tears in Dry Eye	Jacob, Jean T, Ph.D	Louisiana State Univ HSC New Orleans, New Orleans, LA
U10EY013018	Carotenoids & Age-Related Eye Disease In Women's Health	Mares-Perlman, Julie A, MS	University Of Wisconsin Madison, Madison, WI
R03EY014013	In Vivo Imaging of Leukocyte-Endothelial Dynamics	Mathers, William D	Oregon Health & Science University, Portland, OR
R01EY012430	Meibomian Keratoconjunctivitis	Mcculley, James P, MD	University Of Texas SW Med Ctr/Dallas, Dallas, TX
5R01EY007380-14	Interactive Cellular Controls Lacrimal Gland Functional	MENERAY, MICHELE A, Ph.D	Louisiana State Univ HSC New Orleans, New Orleans, LA
5R01EY005801-19	Basal-Lateral/Endomembrane Traffic in Lacrimal Acini	Mircheff, Austin K, BS	University Of Southern California, Los Angeles, CA
5R03EY013720-02	Prolactin--Autocrine/paracrine factor in lacrimal gland	Mircheff, Austin K, BS	University Of Southern California, Los Angeles, CA
5K23EY013766-02	The Contact Lens and Dry Eye Study	NICHOLS, JASON J, OD	Ohio State University, Columbus, OH
5K23EY000393-03	Factors Associated With Dry Eye In Postmenopausal Women	Nichols, Kelly K, OD	Ohio State University, Columbus, OH
5R01EY011915-06	Pathogenesis of Conjunctival Squamous	Pflugfelder, Stephen C, MD	Baylor College Of Medicine, Houston, TX
1R01EY013834-01A1	Molecular Risk Factors for Age-Related Maculopathy	SCHAUMBERG, DEBRA A, OD	Brigham And Women's Hospital, Boston, MA
2R01EY010550-08A2	Prolactin as a Lacrimal Gland Immunoregulator	Schechter, Joel E, Ph.D	University Of Southern California, Los Angeles, CA
5R01EY005612-17	Gender, sex steroids and dry eye syndromes	Sullivan, David A, MS	Schepens Eye Research Institute, Boston, MA
1F33EY014783-01	Analysis of Lacrimal Gland by Laser Microdissection	Ubels, John L, Ph.D	Van Andel Research Institute, Grand Rapids, MI
Z01EY000312-06	The Protective Role of Estrogen in Lens Cataract	Carper, Deborah A.	National Eye Institute/Intramural Program

Title	Abstract
Aquarporin Water Channel Proteins in Eye	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.
Incidence of late macular degeneration in older women	Abstract Text Not Available
Mechanism of Lacrimal Gland Secretion	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.
Female Hormones and Vision	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 Tomograhery. (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.
ECM Regulation by Estrogen in ARMD	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.
Mucins Of The Ocular Surface	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 conjunctivitis 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.
Proteins In Molecular Mechanisms Of Tear Film Formation	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.
Microtubule-Based Transport In Lacrimal Gland Function	A major cause of ocular morbidity in the United States is lacrimal insufficiency, which affects 10 million Americans, primarily women. Approximately one fifth of these cases are clearly autoimmune- mediated and accompanied by additional symptoms that lead to the diagnosis of Sjogren's syndrome. The remainder of cases, designated as Non-Sjogren's lacrimal insufficiency, may also be mediated by the immune system. In the lacrimal gland, defects in membrane trafficking including altered processing of internalized and newly synthesized constituents through the endocytic and secretory pathways have been proposed to contribute to the development of dry eye and the autoimmune disease Sjogren's syndrome. Despite the hypothesis that defective trafficking plays a role in production of autoantigens in the lacrimal gland, little is known about the precise mechanisms by which altered trafficking patterns might occur. In interphase cells, microtubules provide a network that supports the movement of membranes driven by two different cytoplasmic motor proteins, kinesin and cytoplasmic dynein. Despite their importance in

	membrane trafficking, little is known about the involvement of these motors in normal and defective trafficking in the lacrimal gland. The PI has explored the membrane association and in vitro properties of kinesin from lacrimal acinar cells. Preliminary data suggest that kinesin plays a role in secretion under conditions that represent normal function and also under conditions in which traffic has been altered by sustained stimulation. Since such conditions may underlie the initiation of local autoimmune responses that may progress to Sjogren's syndrome or non- Sjogren's lacrimal insufficiency, these findings necessitate a more comprehensive investigation of the role of microtubule-based transport and specifically, kinesin, in lacrimal acinar membrane trafficking. The focus of this proposal is therefore: a. To identify the changes in lacrimal acinar membrane trafficking caused by disruption of microtuble-based motility. b. To define the biochemical properties and membrane interactions of kinesin isolated from lacrimal acinar cells. c. To determine whether stimulation of lacrimal secretion by carbachol, a secretagogue acting through diacylglycerol and Ca2+ -dependent pathways, alters kinesin activity. Once the function of kinesin is defined in resting and stimulated cells from normal rabbits, the PI may begin to question whether kinesin activity is altered in isolated acini from a recently described rabbit model of autoimmune dacryadenitis that exhibits features of Sjogren's syndrome.
Prospective Study Of Risk Factors For Eye Disease	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.
Capillary Electrophoresis Profiling of Tears in Dry Eye	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.
Carotenoids & Age-Related Eye Disease In Women's Health	Despite popular interest in the possibility that the xanthophyll carotenoid lutein, and its structural isomer zeaxanthin, may protect against the onset or progression of age-related macular degeneration, data to support this relationship is insufficient. Data are also accumulating to support a possible protective affect of diet xanthophylls on nuclear cataract. Observational studies that reflect long term relationships of intake of these xanthophyll carotenoids to their accumulation in the retina and the occurrence of these conditions in human populations are needed. We plan to utilize the existing cohort of Women's Health Initiative participants to study the relationships of long term high vs. low dietary intake of xanthophylls to the accumulation of xanthophyll carotenoids in macular pigment and the prevalence of age-related maculopathy and nuclear cataract (the two major determinants of visual impairment in the older adult population). Participants in observational study cohorts of the Women's Health Initiative at these sites (Kaiser Center for Health Sciences in Portland, University of Iowa, Iowa City and University of Wisconsin-Madison) whose xanthophyll intake at study entry was in highest and lowest quintiles will be selected (n=2713). We will compare macular pigment density measured by newly advanced technology using heterochromatic flicker photometry in these groups and evaluate the lifestyle, physical, and diet factors that influence these comparisons. We will also compute odds ratios for age-related maculopathy and nuclear opacities in women with high and low xanthophyl intakes, after adjusting for other known diet, physical and lifestyle factors that may influence these relationships. Results will add to the body of

	evidence needed to make dietary recommendations regarding the benefit of eating diets rich in fruits and vegetables that are rich in xanthophylls. They will also provide information needed about these relationships to conduct sound clinical trials that evaluate the influence of supplements containing these xanthophylls on shorter term progression of age-related eye diseases.
In Vivo Imaging of Leukocyte-Endothelial Dynamics	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.
Meibomian Keratoconjunctivitis	Chronic blepharitis, one of the most common conditions seen in the ophthalmologist's office, is difficult to treat effectively. It is an extremely complex condition that manifests several different and overlapping arrays of signs and symptoms (crusting of lid margin, itching and burning eyelids, lid inflammation, swelling, conjunctival inflammation, localized corneal damage). Evidence indicates that meibomian gland abnormalities are involved in several forms of this disease, principally through their lipid secretions. The basic premise is that biochemical changes of meibomian gland lipids cause many signs directly, while lipid composition itself predisposes secretions to other changes resulting from microbial activity or other factors. Using analytical techniques that allow us to analyze the meibomian secretions from individual patients, understand how chronic blepharitis disease signs are caused by changes in lipid composition, ascertain why the lipid modifications occur, develop new treatments which will reverse or mask the deleterious lipid modifications, define further the structural and physiological characteristics of the tear lipid layer, and define the role lipids (especially the polar lipid phase) play in keratoconjunctivitis. Aim I tests specific hypotheses about the relations between lipid abnormalities in chronic blepharitis and specific mechanisms of action. Aim 2 tests the hypothesis that the relative level of lipid unsaturation, cholesterol and polyol (e.g. sugar, cerebroside) content directly affects meiburn fluidity. Aim 3 tests the hypothesis that infant meibum differs from adult in fatty acid and alcohol type or in polar lipids. Aim 4 tests predictions from the hypothesis that the biophysical characteristics of meibum in the tear film are a direct result of the meibum chemical (lipid) composition. Methods include non-destructive HPLC as well as GC-MS to analyze patient meibum, and standard lipid mixtures based on the composition of patient meibum for physical measurements.
Interactive Cellular Controls Lacrimal Gland Functional	The long term objective of this application is to gain insight into the cellular and molecular controls of lacrimal secretion. The intent of the work is to provide a framework for understanding the pathogenesis of Sjogren's syndrome (SS) and for the development of therapies for dry-eye associated with the disease. The specific aims of this application are designed to test three hypotheses that address 1) the relationship between early changes in the lacrimal gland and the later onset of autoimmune disease and 2) the identification of the cellular and molecular mechanisms that underlie the influence of the hormonal environment on the development and treatment of SS. The first specific aim will test the hypothesis that alterations in the expression or activity of G-protein coupled receptor (GPCR) signaling molecules occur prior to lymphocytic infiltration and result in disruptions in secretion that contribute to the lacrimal insufficiency of SS. Physiologic secretory function, cell-surface receptor-G protein coupling and mRNA and protein expression of G protein subunits, and relevant isoforms of adenylyl cyclase, phospholipase C and protein kinases will be evaluated in pre-autoimmune genetic models of SS and in control animals. The second specific aim will test the hypothesis that the autoimmune response in SS is, in part, precipitated by inappropriate Fas/Fas L mediated apoptosis of epithelial cells of the lacrimal gland. The second aim will also test the hypothesis that the occurrence of apoptosis is influenced by the altered expression or activity of key GPCR signaling molecules. The second aim will be accomplished by the evaluation of apoptosis in lacrimal epithelial cells of genetic models of SS prior to lymphocytic infiltration. The effect of activation or inhibition of GPCR signaling molecules on the occurrence of apoptotic figures and on the mRNA and protein expression of Fas, Fas L and bcl-2 family members will be measured. Alteration of the phosphorylation state of bcl-2 family members by these treatments will also be assessed. The final specific aim will test the hypothesis that the mechanism by which androgens maintain or restore lacrimal function is by influencing the expression or function of GPCR and/or programmed cell death signaling molecules. This will be tested by acute and chronic exposure of lacrimal acinar cells to androgen. Genomic and non-genomic effects of androgen on secretory function and on the expression and activity of signaling molecules will be assessed by similar methods used to accomplish the first and second specific aims.
Basal-Lateral/Endomembrane Traffic in Lacrimal Acini	Primary Lacrimal Deficiency and Sjogren's autoimmune dacryoadenitis are more common in women than men, and the same constellation of hormonal factors, i.e., insufficient bioavailable testosterone and excessive prolactin, may contribute to both pathologies. Lacrimal insufficiency also may occur after refractive surgery. Sjogren's autoimmunity targets the M3 muscarinic receptor, a cell surface protein, and various intracellular proteins. An emerging understanding of traffic between the basal-lateral plasma membranes and endomembrane compartments suggests the immune system may lose its tolerance for familiar proteins, or become activated

	against cryptic proteins, when: (a) changes in traffic increase the rates at which acinar cells express intracellular autoantigens at their blm or secrete them to the interstitium; (b) acinar cells begin to express MHC Class II molecules and present autoantigen peptides directly to CD4 T cells; or (c) the spectrum of immunomodulatory factors acinar cells secrete to the interstitium becomes immunostimulatory instead of immunosuppressive. In vivo experimental perturbations that alter blm / endomembrane traffic include: chronic and supramaximal secretory stimulation, which might arise in vivo as the lacrimal gland - ocular surface servomechanism compensates for lacrimal dysfunction due to androgen insufficiency or prolactin excess; stimulation with epidermal growth factor (EGF), which may be elicited in vivo in response to corneal trauma; and culture in the presence of prolactin, which may mimic high prolactin states. The specific aims of the proposed work are to: 1. Identify membrane protein sorting mechanisms that are altered when lacrimal acinar cells are stimulated with (EGF). 2. Map the traffic of M3 cholinergic receptors; test the hypotheses that acinar cells secrete M3 proteolytic fragments to the interstitium; that acinar cells present M3 peptides to CD4 T cells via MHC Class II molecules; and that chronic stimulation with carbachol decreases M3 receptor turnover, potentially decreasing M3-related antigenic stimulation. 3. Test the hypotheses that a milieu containing excessive prolactin alters protein sorting in the absence and presence of cholinergic stimulation and that excessive prolactin increases turnover of M3 receptors, potentially increasing M3-related antigenic stimulation. 4. Map the traffic of endogenously expressed IL-2 and transduced anti-inflammatory cytokines, such as IL-10. Test the hypotheses that IL-10 alters traffic of endogenous proteins; that chronic stimulation with carbachol in the absence of androgens increases traffic of IL-2 and IL-10 via the apical secretory pathway; and that chronic carbachol stimulation in the presence of androgen increases secretion via the blm.
Prolactin--Autocrine/paracrine factor in lacrimal gland	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.
The Contact Lens and Dry Eye Study	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.
Factors Associated With Dry Eye In Postmenopausal Women	The specific aims of this proposal are as follows: to train Dr. Nichols in the areas of visual epidemiology and biostatistics, to evaluate the systemic and environmental factors associated with dry eye in the Women's Health Initiative Observational Study, and to investigate the relations among dry eye diagnostic tests in this cohort. We plan to utilize the Observational Study (OS) cohort of the Women's Health Initiative (WHI) at The Ohio State University. Approval for this WHI ancillary study has been obtained from the WHI Executive Committee and the WHI Design and Analysis Committee. In an effort to increase statistical power, a dry eye screening survey will be used to enrich the dry eye cases in this cross-section study design (sometimes called a prevalent case-control study). Following the dry eye screening survey, a dry eye examination will be performed on approximately 750 WHI Observational study participants (350 symptomatic patients, and 400

	asymptomatic patients frequency matched by age). The definition of dry eye we will use includes the presence of symptoms of ocular irritation and one of three abnormal dry eye diagnostic tests: tear break-up time, fluorescein staining of the cornea, and measurement of tear meniscus height. Logistic regression will be used to assess the factors associated with a dry eye diagnosis using baseline and year3 follow-up data from the Women's Health Initiative Observational Study cohort. Sensitivity and specificity and Receiver Operating Characteristic (ROC) analyses will be performed to evaluate the relations between the additional diagnostic tests performed in the dry eye examination (osmolality, lactoferrin concentration, phenol red thread test, and lissamine green conjunctival staining) and our proposed definition of dry eye. The training plan and the research plan are closely related in this proposal. The research plan will produce a data set of adequate scope and size to allow Dr. Nichols to apply the epidemiologic and biostatistical theory learned in the classroom. Throughout the course of the training plan, Dr. Nichols will complete the Ph.D. program in Vision Science/Physiological Optics and the Master's in Public Health program with an emphasis in epidemiology and biostatistics at The Ohio State University. Together, the research plan and the training plan will provide Dr. Nichols with the skills and experience needed to excel as a patient-based clinician-scientist.
Pathogenesis of Conjunctival Squamous	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.
Molecular Risk Factors for Age-Related Maculopathy	This is a revised application by a new investigator to assess the role of inflammation in age-related maculopathy (ARM). ARM comprises the leading cause of incurable blindness among older adults in the US and other developed countries. However, the basic molecular pathways involved in the pathogenesis of ARM remain unknown, few potentially modifiable risk factors have been identified, and treatment remains inadequate. We hypothesize that the pathologic changes occurring in both the early and late stages of ARM are mediated by cells and molecules associated with inflammation and that the pro-inflammatory state that gives rise to these changes is at least in part a systemic rather than merely local phenomenon. The proposed studies will build upon a broadly based and growing body of research that supports a key role for inflammatory/immune-mediated processes in ARM pathogenesis. This research suggests several pathways through which inflammation could mediate the development of ARM, including RPE damage and repair, drusen formation, degeneration of Bruch's membrane, endothelial dysfunction in choroidal vessels, increased oxidative stress, decreased bioavailability of antioxidants, as well as the direct or indirect promotion of angiogenesis. Through its use of archived blood specimens from the Physicians'Health Study, Women's Health Study, women's Antioxidant Cardiovascular Disease Study, Nurses' Health Study, and Health Professionals Follow-up Study, this proposal represents an exceptionally cost-effective and efficient means to investigate the proposed hypothesis using a prospective nested case-control study design. The Specific Aims are to investigate 1) the relationship of systemic markers /mediators of inflammation (IL-6, C-reactive protein, fibrinogen, haptoglobin, circulating adhesion molecules, and tumor necrosis factor-alpha receptors) with incident ARM, 2) the separate relationships of these inflammatory molecules with dry and neovascular ARM lesions, 3) whether the relationship of inflammation with ARM is independent of other risk factors such as cigarette smoking, and 4) the interrelationships among the biomarkers and which independently predict incident ARM. These aims will be accomplished through measurement using highly sensitive assays of inflammatory biomarkers in blood specimens collected at baseline (i.e. prior to the development of ARM) and stored since that time below -80xC. Biomarker levels will be compared among subjects who eventually developed ARM and control subjects who remained free of ARM, and the analysis will be extended to control for other risk factors. The long-term objective and clinical relevance of this research is to shed light on potential underlying biological mechanisms of ARM pathogenesis and suggest avenues for new preventive or therapeutic approaches, as well as to identify clinically useful biomarkers for identification of individuals at increased risk of ARM.
Prolactin as a Lacrimal Gland Immunoregulator	Dry eye is one of the most frequently encountered problems in ophthalmology, with highest incidence in women, especially postmenopausal where atrophy and decreased tear formation are associated with chronic inflammation. It also occurs in Sjogren's syndrome, an autoimmune disease characterized by lymphocytic infiltration and loss of lacrimal acinar cells. The hormonal milieu is a critical factor in maintenance of normal lacrimal function, and androgens and prolactin (PRL) both play important roles. We have demonstrated that lacrimal fluid production in rabbits is decreased during pregnancy, and that pregnant women experience increased symptoms of dry eye, worsening with multiple pregnancies. Our studies in rabbits demonstrate dramatic changes in the concentration and distribution of PRL and growth factors within the lacrimal gland (LG) during pregnancy and lactation, increasingly being concentrated within ductal epithelial cells. These changes are accompanied by the appearance of "reactive acinar cells," which are immunopositive for MHC Class II protein and which may also be passive sources of autoantigenic stimulation, and by a marked redistribution of T and B lymphocytes from their normal periductal location to interacinar sites. We propose a new paradigm for physiological regulation of LG function, i.e., an "acinar-ductal loop." In this system, ductal epithelial cells monitor the contents of the acinar effluent, absorb and transport materials from the duct lumen to periductal immune cells, and in so doing function in transmitting immunoregulatory signals (PRL, growth factors, cytokines) that may enhance periductal immune cell activation and responses to autoantigens. We propose to approach this integrated physiological system

	from perspectives of endocrinology and cellular physiology, employing rabbits, and mouse models of Sjogren's syndrome to pursue the following specific aims: (1) Test the hypothesis that lacrimal acinar cells and lacrimal ductal epithelial cells represent a physiological loop, in which ductal epithelial cells monitor acinar fluid contents, absorb and transport materials from within the duct lumen, and function in local immunoregulation. (2) Test the hypothesis that artificially altering the hormonal milieu of non-pregnant rabbits will elicit responses in the LG that are identical to those observed during pregnancy and lactation. (3) Use in vitro methods to characterize the effects of pregnancy, and growth factors whose expression is increased during pregnancy, on secretory function and intracellular autoantigen traffic in lacrimal acinar cells. (4) Test the hypothesis that increased PRL, characteristic of pregnancy and lactation, enhances activation of lymphocytes in the LG. (5) Test the hypothesis that pregnancy accelerates and exacerbates the progress of Sjogren's-like infiltration of the LG in mouse models of Sjogren's syndrome.
Gender, sex steroids and dry eye syndromes	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.
Analysis of Lacrimal Gland by Laser Microdissection	Malfunction of the lacrimal glands causes aqueous deficient dry eye. There is presently no treatment for lacrimal gland disease and progress towards development of effective therapy requires a thorough understanding of lacrimal function. The lacrimal gland is a tubulo-acinar gland with both acinar cells and ducts. The accessory lacrimal glands found in the palpebral and tarsal conjunctiva also produce aqueous tears. Little is known about the function of the lacrimal gland duct epithelium or accessory glands because of their small size and inaccessibility which makes it difficult to separate them from surrounding tissue. The purpose of the proposed study is to explore the feasibility of using laser capture microdissection to isolate and analyze these cell types. The specific aims of the project are to: 1) Sample rat exorbital lacrimal gland duct epithelial cells and accessory lacrimal gland acinar cells by laser capture microdissection, 2) compare gene expression among exorbital gland duct cells, exorbital gland acinar cells and accessory gland cells by gene microarray analysis, 3) identify selected genes that are differentially expressed in these cell types. The results of this study are expected to form the basis for further studies that will clarify the role of duct cells in the secretion and modification of lacrimal fluid and also lead to a better understanding of the role of accessory glands as compared to the main lacrimal gland in tear secretion.
The Protective Role of Estrogen in Lens Cataract	Older women develop more cataracts than 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. Our laboratory has been interested in the protective role of estradiol, and has used the TGF-beta cataract model to examine the effects of TGF-beta and estradiol in lenses from normal male and female rats. 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 level of estrogen receptors. The TGF-beta2 model has many similarities with human anterior subcapsular cataracts and secondary cataracts. Anterior subcapsular cataracts obscure vision, because of their central location in the optical axis. The cataract is the result of an abnormal accumulation of epithelial cells that produce proteins not normally present in the lens, such as, alpha-smooth muscle actin, types I and III collagen, and fibronectin. In secondary cataracts, posterior capsular opacification occurs after cataract surgery as a result of invasion by residual lens epithelial cells. Wrinkling of the capsule and accumulation of extracellular matrix material are hallmarks of this pathology. Secondary cataracts require YAG laser capsulotomy. Therapeutic alternatives that hold promise in retarding lens cell migration include inhibition by thapsigargin, FGF receptor-1, TGF-beta, and integrin antagonists. Estradiol may fall in this category. However, the current study indicates that male-female differences will need to be considered when testing this alternative.

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 (N = 48,836)
2) **Postmenopausal hormone therapy** in preventing coronary heart disease and other cardiovascular diseases, with breast cancer as a possible adverse outcome (N=27,347). 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. (See publications for related papers.) The estrogen-only component of the hormone trial continues.
3) **Calcium and vitamin D supplementation** in preventing osteoporotic fractures (N = 36,282)

Women may participate in one, two, or all three trials. Overall benefit-versus-risk assessment is a central focus in each of the three CT components.

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.

Representative NHLBI Research Projects

Project No.	Title	Investigator	Institution
R01 HL28266	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 HL32050	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 HL33177	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 HL34594	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 HL45666	Cardiovascular Benefits of Soy Phytoestrogens	Clarkson	Wake Forest U.

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

R0l HL57790	CVD Risk & Health in Postmenopausal Phytoestrogen Users	Kritz-Silverstein	U. Cal., San Diego

A study to determine the acceptability and benefits of use of a dietary supplement of phytoestrogen (genistein) versus placebo on heart disease risk factors, bone density, and psychosocial outcomes in postmenopausal women.

R01 HL60739	Mutations, Hormone Therapy and Venous Thromboembolism	Psaty	U. Washington

An assessment of the interaction between HRT and prothrombotic mutations as it affects the incidence of venous thromboembolism.

R01 HL63293	Thrombotic, Inflammatory, & Gene Markers of CVD in Women	Ridker	Brigham & Women's Hospital

A substudy of the WHI observational study exploring inherited and environmental determinants of coronary thrombosis.

P50 HL63494	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 HL67128	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 HL68939	Estrogen, Cytokines and Heart Failure in Women	Reis	University of Pittsburgh

A clinical research study to determine the effects of estrogen therapy on postmenopausal women with congestive heart failure.

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.

Recent Representative Publications

1. Manson JE et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003 Aug 7;349(6):523-34.

2. Hodis HN et al. Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. N Engl J Med 2003 Aug 7;349(6):535-45.

3. Chlebowski RT et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA 2003 Jun 25;289(24):3243-53.

4. Shumaker SA et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 2003 May 28;289(20):2651-62.

5. Rapp SR et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 2003 May 28;289(20):2663-72.

6. Wassertheil-Smoller S et al. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. JAMA 2003 May 28;289(20):2673-84.

7. Waters DD et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. JAMA 2002 Nov 20;288(19):2432-40.

8. Dwyer KM et al. Carotid wall thickness and years since bilateral oophorectomy: the Los Angeles Atherosclerosis Study. Am J Epidemiol 2002 Sep 1;56(5):438-44.

9. Pradhan AD et al. Inflammatory biomarkers, hormone replacement therapy, and incident coronary heart disease: prospective analysis from the Women's Health Initiative Observational Study. JAMA 2002 Aug 28;288(8):980-7.

10. Rossouw JE et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative Randomized Controlled Trial. JAMA 2002 Jul 17;288(3):321-33.

11. Greendale GA et al. Bone mass response to discontinuation of long-term hormone replacement therapy: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Safety Follow-up Study. Arch Intern Med 2002 Mar 25;162(6):665-72.

12. Zhang Y et al. The effect of estrogen use on levels of glucose and insulin and the risk of type 2 diabetes in American Indian postmenopausal women: the Strong Heart Study. Diabetes Care 2002 Mar;25(3):500-4.

13. Sutton-Tyrrell K et al. Subclinical atherosclerosis in multiple vascular beds: an index of atherosclerotic burden evaluated in postmenopausal women. Atherosclerosis 2002 Feb;160(2):407-16.

14. Fang Z et al. Estrogen depletion induces NaCl-sensitive hypertension in female spontaneously hypertensive rats. Am J Physiol Regul Integr Comp Physiol 2001 Dec;281(6):R1934-9.

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 INSTITUE ON AGING

(NIA)

National Institute on Aging

The National Institute on Aging (NIA) supports and conducts research on aging processes, including menopause. This document describes the information that NIA provides to the public and highlights recent menopause-related research findings. It also relays plans for a State of the Science Conference on menopause. A separate spreadsheet lists relevant research grants.

Public Information

The NIA website, www.nia.nih.gov, and the Alzheimer's Disease Education and Referral Center (ADEAR) website, www.alzheimers.org, contain information about menopause. Provided below are online sources and the links to those sites. Print versions of these free publications may be ordered online, by calling 1-800-222-2225, or by writing the NIA Information Center, P.O. Box 8057, Gaithersburg, MD 20898-8057.

- **Menopause: One Woman's Story, Every Woman's Story**

  A 32-page color booklet with information explaining what menopause is and what women can expect to experience. Menopause is a part of every woman's reproductive life cycle. It is not an illness that necessitates treatment. To understand menopause, you first need to understand the whole reproductive process and how your body changes from stage to stage. View the 2001 version of the *Menopause Booklet* at:
  http://www.nia.nih.gov/health/pubs/menopause/menopause.pdf

  In July 2002 the National Heart, Lung, and Blood Institute stopped part of the Women's Health Initiative early due to an increased risk of invasive breast cancer. Since then, more findings from this major clinical trial have been published. For those, go to *Menopause: An Update, 2003* http://www.nia.nih.gov/menopause/menopauseupdate2003.pdf

- **Age Page: Menopause** http://www.niapublications.org/engagepages/menopause.htm

  Menopause, or the "change of life," affects each woman in a different way. This publication describes the changes that are part of this time of life, as well as the symptoms of menopause and what to do about them.

- **Age Page: Hormones after Menopause**
  http://www.niapublications.org/engagepages/hormones.htm

  Millions of women take hormones around the time of menopause. It may or may not be the right choice for any one woman. This age page helps women understand the benefits and risks of menopausal hormone therapy.

- **Age Page: Osteoporosis: The Bone Thief**
  http://www.niapublications.org/engagepages/osteo.htm

  This contains a discussion of osteoporosis—testing, treatment, and prevention.

- **Questions and Answers about the Women's Health Initiative Memory Study—May 2003**

  http://www.nia.nih.gov/menopause2003/faq.htm

These provide information about the findings from WHIMS reported in May 2003.

- **Detailed Questions and Answers about the Women's Health Initiative and the Women's Health Initiative Memory Study—May 2003**

  http://www.nia.nih.gov/menopause2003/faq-detailed.htm

  These provide detailed information about the findings from WHIMS reported in May 2003.

- **Understanding Risk: What Do Those Headlines Really Mean?**
  http://www.niapublications.org/pubs/understanding-risk/index.htm

  Every day in the newspaper or on television we see stories about new medical findings. How are we to make sense of such stories? How do we know what to believe?

Publications Translated into Spanish

- **Menopausia**

  http://www.niapublications.org/spnagepages/menopause-sp.htm

- **Preguntas y respuestas acerca de la Iniciativa de Salud de la Mujer (Women's Health Initiative-WHI) y sobre el estudio sobre la memoria de la WHI—Mayo 2003**

  http://www.alzheimers.org/nianews/Q&Aespanol56.htm

- **Preguntas y respuestas detalladas acerca de la Iniciativa de Salud de la Mujer (Women's Health Initiative-WHI) y sobre el estudio sobre la memoria de la WHI—Mayo 2003**

  http://www.alzheimers.org/nianews/Q&Aadicionales56.htm

Highlights of Research Related to Menopause

EXTRAMURAL

Study of Women's Health Across the Nation (SWAN)
Funded initially in 1994 by the National Institute on Aging, National Institute of Nursing Research and the Office of Research on Women's Health, the *Study of Women's Health Across the Nation* (SWAN) is a longitudinal study of the natural history of the female mid-life, including the menopausal transition. (Ancillary studies are supported by the National Institute of Mental Health, National Heart Lung and Blood Institute, and the National Center for Complementary and Alternative Medicine.) SWAN is a multi-site, multi-ethnic, multi-disciplinary study of African American, Caucasian, Chinese, Japanese and Hispanic women of the chronology of biological and psychosocial characteristics. SWAN seeks to describe the effect of the menopause transition and its associated characteristics on subsequent health and risk factors for age related chronic diseases. More than 3200 women enrolled in the study.

SWAN: Racial and Ethnic Differences in DHEAS Levels During the Menopause Transition

There is wide-spread belief that dehydroepiandrosterone sulfate (DHEAS) may play a role in preventing diseases of aging because (1) it is an abundant circulating steroid product that is potentially an important androgen and estrogen precursor, and (2) more than 80% of its secretion declines between the ages of 20 and 70 years as incidence of the chronic diseases of aging increases. Because DHEAS replacement studies have reported some beneficial, but inconsistent, effects related to immune function, mood and other outcomes, the role of DHEAS in the aging process remains an intriguing biological question. Data from SWAN indicate significant ethnic/racial differences, with the highest levels found among Chinese and Japanese women and lowest levels found among African-American and Hispanic women. Interestingly, circulating DHEAS levels did not decline at a steady rate during the menopausal transition, and in fact, actually increased transiently (especially during the transition to late perimenopause) in some women. Changes in circulating testosterone, and to a lesser extent, estradiol were correlated to changes in DHEAS. These data are important in understanding the endocrinology of the menopause transition, defining the relationship of adrenal steroid production during declining ovarian function and determining a rationale regarding supplementation with DHEAS or other androgens for older women.

Lasley BL, Santoro N, Randolf JF, Gold EB, Crawford S, Weiss G, et al. The relationship of circulating dehydroepiandrosterone, testosterone, and estradiol to stages of the menopausal transition and ethnicity. *J Clin Endocrinol Metab* 2002;87(8):3760-7

SWAN: Ethnic Group Differences in Bone Density May Explain Differences in Risk of Fracture

Bone mineral density (BMD) and fracture rates vary among women of differing ethnicities. Most reports suggest that BMD is highest in African-Americans, lowest in Asians, and intermediate in Caucasians, yet Asians have lower fracture rates than Caucasians. To assess the contributions of anthropometric and lifestyle characteristics to ethnic differences in BMD, lumbar spine and femoral neck BMD was assessed by dual-energy x-ray absorptiometry in over 2200 premenopausal or early perimenopausal women (mean age, 46.2 yr) participating in SWAN. Before adjustment for covariates, lumbar spine and femoral neck BMDs were highest in African-American women, next highest in Caucasian women, and lowest in Chinese and Japanese women. Unadjusted lumbar spine and femoral neck BMDs were 7-12% and 14-24% higher, respectively, in African-American women than in Caucasians, Japanese, or Chinese women. After adjustment, lumbar spine and femoral neck BMD remained highest in African-American women, and there were no significant differences between the remaining groups. When BMD was assessed in a subset of women weighing less than 70 kg, lumbar spine BMD became similar in African-American, Chinese, and Japanese women and was lowest in Caucasian women. Femoral neck BMD was highest in African-Americans and similar in Chinese, Japanese, and Caucasians. It was concluded that among women of comparable weights, there are no differences in lumbar spine BMD among African-American, Chinese, and Japanese women, all of whom have higher BMDs than Caucasians. These findings may explain why Caucasian women have higher fracture rates than African-Americans and Asians.

Finkelstein JS, Lee ML, Sowers M, Ettinger B, Neer RM, Kelsey JL, et al. Ethnic variation in bone density in premenopausal and early perimenopausal women: effects of anthropometric and lifestyle factors. J Clin Endocrinol Metab 2002;87(7):3057-67.

Biology of Aging: New Agents Stimulate Bone Formation in Mice

Researchers, working on new agents to stimulate bone formation through the estrogen receptor, have shown that stimulation of the estrogen (and androgen) receptor leads to two pathways inside the cell: the "genotropic" pathway where the receptor interacts at the nucleus and stimulates the classical sex-organ specific responses, and a second, less understood pathway that inhibits cell death in osteoblasts. The agents, in a class termed ANGELS by the researchers, stimulate only the second pathway, inhibiting osteoblasts cell death and stimulating bone formation in mice, while having no discernable effect on the sex organs (because the ANGELS do not operate through that pathway). The mechanism of action is different from that of the selective estrogen receptor modulator (SERM), raloxifene and offers a new pathway to investigate potential treatments that not only maintain bone, but actually build bone, and that may be effective for both males and females.

Kousteni S, Han L, Chen, J, Almeida M, Plotkin LI, Bellido T Manolagas SC. Kinase-mediated regulation of common transcription factors accounts for the bone-protective effects of sex steroids. J Clin Invest. 2003 Jun; 111(11):1651-64.

Kousteni s, Chen J, Bellido T, Han L, Ali AA, O'Brien CA, Plotkin L, Fu Q, Mancino AT, Wen Y, Vertino AM, Powers CC, Stewart SA, Ebert R, Parfitt AM, Weinstein RS, Jilka RL, Manolagas SC. Reversal of bone loss in mice by nongenotropic signaling of sex steroids. Science. 2002, Oct 25;298(5594):843-6. Erratum in: Science. 2003 Feb 21;299(5610):1184.

Kousteni S, Bellido T, Plotkin LI, O'Brien CA, Bodenner DL, Han L, Han K, DiGregorio GB, Katzenellenbogen J.A., Katzenellenbogen BS, Roberson PK, Weinstein RS, Jilka RL, Manolagas SC. Nongenotropic, sex-nonspecific signaling through the estrogen or androgen receptors: dissociation from transcriptional activity. Cell. 2001 Mar 9;104(5):719-30.

INTRAMURAL

Research in Non-Human Primates

Studies are ongoing to ascertain the impact of calorie restriction (CR) on the process of aging, including the age-related decline in the female reproductive axis. Monkeys on CR receive 30 percent less of a highly nutritious diet compared to controls. In one of the two components of this project, females have been maintained on CR for more than a decade. These females began CR either when they were young or in early adulthood. These females are now middle-aged to aged, facilitating study of the climacteric in CR primates. Hormone measurements of ovarian steroids along with monitoring menstrual cycles reveal that a similar number of females are experiencing perimenopausal irregularity of the menstrual cycle. At this point in the study, there appears to be lower incidence of endometriosis in CR females, based on the presence or absence of clinical manifestations related to this condition. Based on the data at this time, CR may reduce the incidence of endometriosis and may have benefits in the process of perimenopause.

Genes Associated with Premature Ovarian Failure

About 1-3% of women undergo early menopause rather than reaching the usual reproductive lifespan at about age 50. A fraction of such instances of early-onset "premature ovarian failure" (POF) is genetic in origin. A single locus on chromosome 3 is implicated in several families and a number of isolated individuals, with translocations or deletions that interrupt the DNA in that region. NIA intramural researchers have isolated the gene FOXL2. Mutations in FOXL2 cause POF, making it the first gene shown to be responsible for POF in humans.

Crisponi L, Deiana M, Loi A, Chiappe F, Uda M, Amati P, Bisceglia L, Zelande L, Nagaraja R, Porcu S, Ristaldi MS, Marzella R, Rochhi M., Nicolino M, Lienhardt-Roussie A, Nivelon A, Verloes A, Schlessinger D, Gasparini P, Bonneau D, Cao A & Pilia G. The putative forkhead transcription factor *FOXL2* is mutated in blepharophimosis/ptosis/epicanthus inversus syndrome. Nature Genetics 2001; 27:159-166

Study of Women through the Menopausal Transition in the Baltimore Longitudinal Study of Aging: Effects on Cognition

NIA scientists have examined cognition in women participating in the Baltimore Longitudinal Study of Aging study of the perimenopause and menopausal transition. Although age-matched pre- and postmenopausal women in the study showed similar cognitive performance, some symptoms associated with the menopause, such as sleep disturbance, had negative effects on specific aspects of cognition, including memory.

NIA Proposes FY 2004 State of the Science Conference: Management of Menopause-Related Symptoms

---

Symptoms, especially vasomotor symptoms, are very common during the menopause transition and may affect as many as two-thirds of all postmenopausal women, although frequencies differ significantly by race/ethnicity and other factors. For several decades, estrogen (alone or in combination with a progestin for women with an intact uterus) as menopausal hormone therapy (MHT) has been the drug of choice for alleviating several menopause-related symptoms because of the lack of alternative therapies of comparable proven efficacy.

In the late 1980's enthusiasm for long-term use MHT was kindled by the growing belief, based on observational studies, that MHT had significant anti-aging potential and represented a preventive strategy for reducing the risk of chronic diseases of aging such coronary heart disease, osteoporotic fractures and even Alzheimer's disease. The Women's Health Initiative (WHI) was designed, funded and ultimately fielded by the NIH in 1993 to evaluate the effects of MHT and other strategies on the risk of cardiovascular disease, breast and colorectal cancer and osteoporotic fractures. In the early summer of 2002, the estrogen-progestin (E+P) arm of the Women's Health Initiative was stopped early (after 5.2 years) because the risks of E+P (increases in breast cancer, coronary heart disease, stroke and pulmonary embolism) were deemed to outweigh the benefits of a reduced risk of osteoporotic fractures and colon cancer.

In October 2002, a Scientific Workshop on Menopausal Hormone Therapy was convened in Bethesda by the NIH. The stated aims of the workshop were to "…place the WHI E+P clinical trial results and

reasons for stopping the trial in the context of other federally funded studies and to help clinicians and their patients better understand the current information on the risks and benefits of short- and long-term use of combination HT."[a] After review of key findings from the WHI and other relevant large-scale long-term studies of MHT, participants at the meeting concluded that the long-term use of combination E+P has no role in the prevention of cardiovascular disease and should be discontinued if it was being used for this purpose.

With respect to the indication of long-term use for reduction of the risk of osteoporotic fractures, it was recommended that postmenopausal women taking E+P to prevent bone loss seek advice on alternative, efficacious strategies from their health care providers. Support for the recommended use of combined MHT was confined to its use at the lowest possible dosages for the short-term management of menopause-related symptoms. However, time did not permit an examination of many of the significant questions and issues surrounding the nature of menopause-related symptoms and the short-term use of MHT for this indication.

Consequently, the NIA proposed to sponsor a State-of-the-Science Conference: "Management of Menopause-Related Symptoms." This conference, co-sponsored by the NIH Office of Research on Women's Health and the National Center for Complementary and Alternative Medicine, will

- Review the nature of menopause-related symptomatology in the context of ovarian aging and senescence and the surrounding biologic, psychosocial and behavioral milieu of the perimenopausal woman.

- Evaluate the role of hormonal and non-hormonal approaches for ameliorating menopause-related symptoms with respect to the efficacy, acceptability, safety and risks/benefits associated with the various approaches.

- Identify opportunities for future research aimed at developing new strategies to treat menopause-related symptoms.

A careful examination of current and potential strategies for the management of menopause-related symptoms will help address some of the most common and salient health-related issues preoccupying midlife women and health care providers seeking to maximize quality of life during the peri- and early postmenopause. Updating the 1979 NIA-sponsored Consensus Development Conference on "Estrogen Use and Postmenopausal Women" will be tremendously valuable in helping clarify some of the recent confusion stemming from the controversial findings from the WHI.

[a] Kirschstein R. Menopausal hormone therapy: summary of a scientific workshop. Ann Intern Med 2003;138(4):361-4

FY 2002 NIA -- Menopause Related Research

		GRANT_NO		PI_NAME	TITLE	LOCATION
5	T32	AG000265	04	CARNES, MARY	WOMEN'S HEALTH AND AGING: RESEARCH & LEADERSHIP TRAINING	UNIVERSITY OF WISCONSIN MADISON
5	K01	AG000879	04	WEGESIN, DOMONICK	HORMONE REPLACEMENT AND AGING EFFECTS ON MEMORY	COLUMBIA UNIVERSITY HEALTH SCIENCES
5	P01	AG004875	19	RIGGS, BYRON	PHYSIOLOGY OF BONE METABOLISM IN AN AGING POPULATION	MAYO CLINIC ROCHESTER
5	R37	AG005233	15	FREEDMAN, ROBERT	BEHAVIORAL TREATMENT OF MENOPAUSAL HOT FLASHES	WAYNE STATE UNIVERSITY
3	R37	AG005233	15S1	FREEDMAN, ROBERT	BEHAVIORAL TREATMENT OF MENOPAUSAL HOT FLASHES	WAYNE STATE UNIVERSITY
2	R01	AG009214	10	RANCE, NAOMI	REPRODUCTIVE AGING AND THE HUMAN HYPOTHALAMUS	UNIVERSITY OF ARIZONA
5	R01	AG012222	08	SANTORO, NANETTE	REPRODUCTIVE PHYSIOLOGY OF OVARIAN FAILURE	YESHIVA UNIVERSITY
5	U01	AG012495	09	MCCONNELL, DANIEL	WOMENS HEALTH ACROSS THE NATION--ENDOCRINE LAB	UNIVERSITY OF MICHIGAN AT ANN ARBOR
5	U01	AG012505	09	POWELL, LYNDA	WOMENS HEALTH ACROSS THE NATION--CHICAGO	RUSH-PRESBYTERIAN-ST LUKES MEDICAL CTR
5	U01	AG012531	09	FINKELSTEIN, JOEL	WOMANS HEALTH ACROSS THE NATION MGH	MASSACHUSETTS GENERAL HOSPITAL
5	U01	AG012539	09	GREENDALE, GAIL	WOMENS HEALTH ACROSS THE NATION--UCLA	UNIVERSITY OF CALIFORNIA LOS ANGELES
5	U01	AG012546	09	MATTHEWS, KAREN	WOMENS HEALTH ACROSS THE NATION--PITTSBURGH	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
3	U01	AG012546	09S1	MATTHEWS, KAREN	WOMENS HEALTH ACROSS THE NATION--PITTSBURGH	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
3	U01	AG012546	09S2	MATTHEWS, KAREN	WOMENS HEALTH ACROSS THE NATION--PITTSBURGH	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
3	U01	AG012546	09S3	MATTHEWS, KAREN	WOMENS HEALTH ACROSS THE NATION--PITTSBURGH	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
3	U01	AG012546	09S4	MATTHEWS, KAREN	WOMENS HEALTH ACROSS THE NATION--PITTSBURGH	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
5	U01	AG012553	09	MCKINLAY, SONJA	WOMENS HEALTH ACROSS THE NATION--CC	NEW ENGLAND RESEARCH INSTITUTES, INC.

5	U01	AG012554	09	GOLD, ELLEN	WOMENS HEALTH ACROSS THE NATION--UCDAVIS	UNIVERSITY OF CALIFORNIA DAVIS
2	R01	AG012611	08	JANOWSKY, JERI	THE ROLE OF SEX HORMONES ON COGNITION	OREGON HEALTH & SCIENCE UNIVERSITY
3	R01	AG012611	08S1	JANOWSKY, JERI	THE ROLE OF SEX HORMONES ON COGNITION	OREGON HEALTH & SCIENCE UNIVERSITY
5	R01	AG012745	07	FREEMAN, ELLEN	EPIDEMIOLOGIC STUDY OF THE LATE REPRODUCTIVE YEARS	UNIVERSITY OF PENNSYLVANIA
5	R01	AG013038	07	SEALS, DOUGLAS	SODIUM RESTRICTION & ARTERIAL COMPLIANCE IN OLDER HUMANS	UNIVERSITY OF COLORADO AT BOULDER
2	R01	AG013204	06A1	VOYTKO, MARY	COGNITION AND ESTROGEN IN MENOPAUSE: A MONKEY MODEL	WAKE FOREST UNIVERSITY HEALTH SCIENCES
5	R29	AG013873	05	SALAMONE, LORAN	GENETIC & LIFE-STYLE FACTORS IN MENOPAUSAL BONE DENSITY	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
5	R01	AG014108	05	TYRRELL, KIM	VASCULAR STIFFNESS AND EFFECTS OF DIETARY INTERVENTION	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
2	R01	AG014124	06	YOUNG, TERRY	MENOPAUSE AND MIDLIFE AGING EFFECTS ON SLEEP DISORDERS	UNIVERSITY OF WISCONSIN MADISON
5	R01	AG014673	05	SCHUPF, NICOLE	EPIDEMIOLOGY OF MENOPAUSE AND DEMENTIA IN DOWN SYNDROME	INSTITUTE FOR BASIC RES IN DEV DISABIL
5	R01	AG014799	06	VELDHUIS, JOHANNES	THE AGING GH AXIS IN POSTMENOPAUSAL WOMEN	UNIVERSITY OF VIRGINIA CHARLOTTESVILLE
5	R29	AG015026	05	WANG, CHING-YUN	MISSING DATA, MEASUREMENT ERROR AND APPLICATIONS	FRED HUTCHINSON CANCER RESEARCH CENTER
5	R29	AG015121	04	SITES, CYNTHIA	HORMONE REPLACEMENT AND METABOLIC CARDIOVASCULAR RISK	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE
5	R01	AG015325	05	ALOIA, JOHN	VITAMIN D SUPPLEMENTATION IN POSTMENOPAUSAL WOMEN	WINTHROP-UNIVERSITY HOSPITAL
2	R01	AG015386	05	KLINE, JENNIE	EPIDEMIOLOGY OF OVARIAN AGE	NEW YORK STATE PSYCHIATRIC INSTITUTE
5	R29	AG015425	06	SEIFER, DAVID	BIOLOGICAL BASIS OF THE PERIMENOPAUSE	UNIV OF MED/DENT NJ-R W JOHNSON MED SCH
5	R01	AG015857	03	CHAUDHURI, GAUTAM	ROLE OF NO AND ESTRADIOL IN AGING AND ATHEROGENESIS	UNIVERSITY OF CALIFORNIA LOS ANGELES
5	R01	AG015947	05	GALLAGHER, MICHELA	ESTROGEN EFFECTS ON AGE RELATED COGNITIVE DECLINE	JOHNS HOPKINS UNIVERSITY
5	P01	AG016765	04	MORRISON, JOHN	ESTROGEN AND THE AGING BRAIN	MOUNT SINAI SCHOOL OF MEDICINE OF NYU

5	R01	AG017057	02	NEWTON, KATHERINE	ALTERNATIVE THERAPIES FOR MENOPAUSE: A RANDOMIZED TRIAL	CENTER FOR HEALTH STUDIES
3	R01	AG017057	02S1	NEWTON, KATHERINE	ALTERNATIVE THERAPIES FOR MENOPAUSE: A RANDOMIZED TRIAL	CENTER FOR HEALTH STUDIES
5	R01	AG017104	03	SOWERS, MARYFRAN	FUNCTIONAL STATUS AND THE MENOPAUSAL TRANSITION	UNIVERSITY OF MICHIGAN AT ANN ARBOR
7	P01	AG017164	03	WISE, PHYLLIS	FEMALE REPRODUCTIVE AGING: THE ROLE OF ESTROGEN	UNIVERSITY OF CALIFORNIA DAVIS
7	P01	AG017164	03	WISE, PHYLLIS	FEMALE REPRODUCTIVE AGING: THE ROLE OF ESTROGEN	UNIVERSITY OF CALIFORNIA DAVIS
5	R01	AG017170	04	STRIKER, LILIANE	ESTROGEN DEFICIENCY AND RENAL DISEASE IN AGING WOMEN	UNIVERSITY OF MIAMI
2	R44	AG017413	02	NICHOLS, LARRY	A ONE YEAR ESTROGEN/PROGESTIN IMPLANT	BIOTEK, INC.
5	R01	AG017496	03	DOTY, RICHARD	POSTMENOPAUSAL ESTROGEN INFLUENCES ON OLFACTION	UNIVERSITY OF PENNSYLVANIA
5	R01	AG017521	03	BAHR, JANICE	EFFECT OF SOYBEANS ON BONE AND THE REPRODUCTIVE TRACT	UNIVERSITY OF ILLINOIS URBANA-CHAMPAIGN
5	R01	AG017578	03	OBERMEYER, CARLA	THERAPEUTIC DECISIONS AT MENOPAUSE--A MULTISITE STUDY	HARVARD UNIVERSITY (SCH OF PUBLIC HLTH)
5	R03	AG017655	02	RAMIREZ, MICHELLE	MENOPAUSE: MEANING AND EXPERIENCE IN OAXACA, MEXICO	UNIVERSITY OF IOWA
5	U01	AG017719	03	SOWERS, MARYFRAN	SWAN REPOSITORY	UNIVERSITY OF MICHIGAN AT ANN ARBOR
5	R01	AG017864	03	WILLIAMS, JAMES	PROGESTOGENS VS PHYTOESTROGENS-- AN ADJUNCT TO ERT	WAKE FOREST UNIVERSITY HEALTH SCIENCES
5	R01	AG017907	03	POLAN, MARY	COLLAGENOLYSIS AS FUNCTION OF MMPS IN INCONTINENT WOMEN	STANFORD UNIVERSITY
5	R01	AG018198	03	KOHRT, WENDY	MODULATION OF VISCERAL FAT BY ESTROGENS AFTER MENOPAUSE	UNIVERSITY OF COLORADO HLTH SCIENCES CTR
5	R01	AG018238	03	CEFALU, WILLIAM	HORMONE REPLACEMENT FOR PREVENTION OF VISCERAL OBESITY	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE
5	R01	AG018239	03	GEISELMAN, PAULA	OBESITY PREVENTION AFTER SMOKING CESSATION IN MENOPAUSE	LSU PENNINGTON BIOMEDICAL RESEARCH CTR
5	R01	AG018400	02	FLAWS, JODI	RISK FACTORS FOR HOT FLASHES IN MID-LIFE	UNIVERSITY OF MARYLAND BALT PROF SCHOOL

5	R01	AG018408	03	GOLDBERG, ANDREW	MENOPAUSE, LPL GENOTYPE AND METABOLISM AFTER WEIGHT LOSS	UNIVERSITY OF MARYLAND BALT PROF SCHOOL
5	R01	AG018798	02	HODIS, HOWARD	ESTROGEN IN THE PREVENTION OF ATHEROSCLEROSIS TRIAL	UNIVERSITY OF SOUTHERN CALIFORNIA
5	K01	AG019164	02	KEENAN, DANIEL	PREDICTING ONSET AGE AND LENGTH OF MENOPAUSAL TRANSITION	UNIVERSITY OF VIRGINIA CHARLOTTESVILLE
5	R01	AG019291	02	SANDBERG, KATHRYN	HORMONAL REGULATION OF ANGIOTENSIN RECEPTORS	GEORGETOWN UNIVERSITY
5	R01	AG019310	02	RYAN, ALICE	DIET AND EXERCISE: RACE, POSTMENOPAUSE AND METABOLISM	UNIVERSITY OF MARYLAND BALT PROF SCHOOL
1	R01	AG019325	01A1	WONG, WILLIAM	SOY ISOFLAVONES ON NO PRODUCTION IN POSTMENOPAUSAL WOMEN	BAYLOR COLLEGE OF MEDICINE
7	R01	AG019327	02	KNOWLTON, ANNE	AGING, ESTROGEN, HSPS AND MYOCARDIAL ISCHEMIA	UNIVERSITY OF CALIFORNIA DAVIS
1	R01	AG019360	01A1	SOWERS, MARYFRAN	SLEEP DURING THE PERIMENOPAUSE IN A MULTI-ETHNIC COHORT	UNIVERSITY OF MICHIGAN AT ANN ARBOR
1	R01	AG019361	01A1	GOLD, ELLEN	SLEEP DURING THE PERIMENOPAUSE IN A MULTI-ETHNIC COHORTS	UNIVERSITY OF CALIFORNIA DAVIS
1	R01	AG019362	01A1	HALL, MARTICA	SLEEP DURING THE PERIMENOPAUSE IN A MULTI-ETHNIC COHORTS	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
1	R01	AG019363	01A1	KRAVITZ, HOWARD	SLEEP DURING THE PERIMENOPAUSE IN A MULTI-ETHNIC COHORT	RUSH-PRESBYTERIAN-ST LUKES MEDICAL CTR
1	K01	AG019630	01A1	VAN PELT, RACHAEL	ESTROGEN, INSULIN AND REGIONAL LIPOLYSIS IN OLDER WOMEN	UNIVERSITY OF COLORADO HLTH SCIENCES CTR
1	R15	AG019648	01A1	AUDESIRK, TERESA	EFFECT OF RALOXIFENE ON NEURONAL PHYSIOLOGY	UNIVERSITY OF COLORADO AT DENVER
1	R01	AG020082	01	MOE, KAREN	PROGESTERONE AND SLEEP IN OLDER WOMEN	UNIVERSITY OF WASHINGTON
1	R01	AG020256	01	HINOJOSA-LABORDE, CARMEN	ESTROGEN AND SODIUM MODULATE HYPERTENSION IN AGING RATS	UNIVERSITY OF TEXAS HLTH SCI CTR SAN ANT
1	R01	AG020583	01	NICKLAS, BARBARA	EXERCISE AND REGIONAL FAT METABOLISM AFTER MENOPAUSE	WAKE FOREST UNIVERSITY HEALTH SCIENCES
1	K01	AG020683	01	MOREAU, KERRIE	HRT AND EXERCISE EFFECTS ON CENTRAL ARTERIAL COMPLIANCE	UNIVERSITY OF COLORADO AT BOULDER
1	R03	AG021250	01	HALVORSON, LISA	ANTERIOR PITUITARY GLAND IN FEMALE REPRODUCTIVE AGING	UNIVERSITY OF TEXAS SW MED CTR/DALLAS

1	R03	AG021300	01	LIU, GANG	FREE IRON, ESTROGEN AND POSTMENOPAUSAL OSTEOPOROSIS	UNIVERSITY OF UTAH
1	U01	AG021382	01	ZELINSKI-WOOTEN, MARY	OVARIAN ASPECTS OF CALORIC RESTRICTION	OREGON HEALTH & SCIENCE UNIVERSITY
1	R03	AG021653	01	FRENKEL, SALLY	ESTROGEN: CHRODROPROTECTIVE OR DESTRUCTIVE?	HOSPITAL FOR JOINT DISEASES ORTHO INST
2	N01	AG092115	05	(Contract)	HORMONE REPLACEMENT THERAPY-COGNITIVE AGING IN WHIMS--FORWARD FUNDED 03-04	
5	R29	HD037360	04	KLEIN, NANCY	AGING OF THE NORMAL HUMAN OVARY FROM BIRTH TO MENOPAUSE	UNIVERSITY OF WASHINGTON
1	Z01	AG000191	06	RESNICK, SUSAN M	NEUROIMAGING PREDICTORS OF COGNITIVE CHANGE AND RESPONSE TO THERAPY	NIA INTRAMURAL
1	Z01	AG000192	02	MAKI, PAULINE	EFFECTS OF SEX STERIOD HORMONES ON COGNITION AND BRAIN FUNCTION	NIA INTRAMURAL
1	Z01	AG000293	13	METTER, E JEFFREY	BIOCHEMICAL PARAMETERS OF BONE METABOLISM: AGE AND SEX CONTRASTS	NIA INTRAMURAL
1	Z01	AG000647	05	NAGARAJA, RAMAIAH	TRANSLOCATION/GENES ASSOCIATED WITH PREMATURE OVARIAN FAILURE	NIA INTRAMURAL

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

(NIAAA)

National Institute on Alcohol Abuse and Alcoholism

Menopause Related Grants

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
AA011184	Gavaler, Judith S.	Alcohol and Estrogen Replacement Therapy Interactions	University of Pittsburgh	APPLICANTS ABSTRACT: By 1991 census data there are 33 million women age 50 and older, the median age at which natural menopause occurs. With the addition of surgical menopause women, there are over 40 million postmenopausal women. Estimates of the prevalence of Estrogen Replacement Therapy (ERT) use range from 12 to 33 to 45%. Estimated current moderate alcoholic beverage consumption among women age 50-60 is 59% and 37% among women over 60. Thus to 5 to 18 million are being treated with ERT, while as many as 20 million potsmenopause (PMP) women drink moderately. The number of postmenopausal who both drink and use ERT is unknown. Both ERT therapy and moderate alcohol consumption increase PMP estrogen levels; both ERT and moderate alcohol consumption significantly reduce coronary heart disease risk, the major cause of death in PMP women. There are 3 goals, of the proposed research: 1) To determine the patterns of alcohol consumption of health behaviors such as smoking, dietary habits/ nutrient intake and physical activity, and of estrogen replacement therapy (ERT) use among 1250 normal PMP volunteers of different ethnic/racial backgrounds participating in a study determinants of PMP estrogen levels. 2) To determine in normal PMP women not treated with ERT whether smoking, physical activity, nutrient intake and ethnical/racial origin influence PMP estrogen levels in addition to already identified estrogen determinants which include moderate alcohol beverage consumption, body fat mass, and ovariectomy. 3) To determine in normal PMP women related with ERT to what degree circulating levels of estrogen achieved with estrogen replacement therapy are modulated by factors which influence the production and metabolism of estrogen and other hormones in PMP women.
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.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

(NIAID)

National Institute on 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 AI 051880, 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. **Gender-specific T cell homing and autoimmunity, R01 AI 042753, PI: Bruce Richardson, University of Michigan**

   Women are more susceptible to autoimmune diseases, and the reason is unknown. Female sex hormones appear to play a role in this predisposition to autoimmunity, but extensive analysis of the effects of the female sex steroids on immune responses in vitro have failed to identify the mechanism(s). This project explores the hypothesis that gender-specific differences in T cell homing, due to effects of female sex hormones on adhesion molecule expression, contribute to increased severity of autoimmune diseases in females by modifying

lymphocyte trafficking patterns. Gender-specific trafficking differences could be important both in the induction of disease as well as later in the disease process. These studies will identify novel and important mechanisms contributing to the increased incidence and severity of autoimmune disease in women.

NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

(NIAMS)

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Menopause Related Grants

Overview

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports basic, clinical, and epidemiological research, research training, and information programs on many of the more debilitating diseases affecting Americans. NIAMS supports research on a number of diseases which disproportionately affect women including: osteoporosis, rheumatoid arthritis, temporomandibular joint disorders (TMJ), systemic lupus erythematosus (lupus), osteoarthritis, and scleroderma. Lupus, osteoarthritis, and scleroderma are diseases in which health disparities have been clearly identified. The NIAMS is committed to uncovering the bases of these gender, racial, and ethnic disparities and to devising effective strategies to treat or prevent them.

Osteoporosis is a skeletal disorder marked by reduced bone strength that predisposes a person to an increased risk of fractures. Among the bone diseases that afflict Americans, osteoporosis is by far the most prevalent, and it is a major health risk for 28 million Americans. It has been estimated that some 10 million women in the U.S. have osteoporosis and another 18 million have low bone mass and are at risk for osteoporosis. The burden of health care costs due to osteoporosis is estimated to be $10 to $15 billion per year.

Osteoporosis continues to be a significant public health challenge for women, particularly after menopause. New hope for those with osteoporosis has come with the approval of a parathyroid hormone (PTH) derivative to treat osteoporosis. The agent, teriparatide, has been shown to reduce the risk of both vertebral and nonvertebral fractures in addition to stimulating bone formation and increasing bone mass. NIAMS supported research has demonstrated that therapeutic approaches using teriparatide and bisphosphonates can restore critical bone loss. This is a significant advance over earlier approaches that depended on hormone therapy to prevent bone loss in post-menopausal women. Researchers have made new advances in understanding the impact of hormonal changes on bone health and understanding the genetic factors associated with osteoporosis. Two clinical assessment tools that may be used to predict fracture risk have also been developed. NIAMS-supported researchers have also shed new light on the relationship between dietary protein intake and bone mineral density in the elderly.

The NIAMS supports a portfolio of grants focused on understanding osteoporosis and seeking ways both to prevent and to treat this disabling condition.

rant Number	PI Name	Project Title	Institution	Abstract
AR002074	KARLSON, ELIZAETH W.	ANTIOXIDANTS AND FEMALE HORMONES IN THE ETIOLOGY OF RA	BRIGHAM AND WOMEN'S HOSPITAL	The candidate is an Instructor in Medicine in the Department of Medicine, Division of Rheumatology, Immunology and Allergy at the Brigham and Women's Hospital and Harvard Medical School. Her research area is the epidemiology of rheumatic diseases, and the social and biological determinants of outcome in rheumatic diseases. Dr. Matthew Liang, Director, Multipurpose Arthritis and Musculoskeletal Diseases Center (MAMDC), Professor of Medicine at Harvard Medical School and Professor of Health Policy and Management at Harvard School of Public Health, will be her sponsor and co-mentor along with Drs. Frank Speizer, Charles Hennekens, Walter Willett and Meir Stampfer from the Channing Laboratory and Division of Preventive Medicine. The research training program consists of the two studies described below, Research Seminars in the MAMDC, Channing Laboratory and Division of Preventive Medicine, courses at the Harvard School of Public Health, and close review by an Advisory Committee. The goal of the proposed studies is to define the role of dietary and hormonal risk factors in the development of rheumatoid arthritis (RA) in women. Specifically, it will test the potential protective role of antioxidants and N-3 fatty acids on the risk of RA, whether postmenopausal estrogen reduces risk and whether menopause increases risk of RA. The study utilizes information from two separate, complementary cohorts, the Nurses' Health Study, a prospective cohort of 121,700 women aged 30-55 years at baseline, followed since 1976, and the Women's Health Study, a randomized, double-blind, placebo-controlled trial of nelow-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer among 39,876 female health professionals, aged 45 years and older. RA will be confirmed by a screening questionnaire regarding rheumatic symptoms and review of medical records. The study will identify potentially modifiable risk factors for primary prevention of RA.
AR002113	DAVIS, JOHN C.	ANDROGEN AS ADJUNCT THERAPY IN RHEUMATOID ARTHRITIS	UNIVERSITY OF CALIFORNIA SAN FRANCISCO	Rheumatoid arthritis (RA) is a chronic, debilitating multisystem disease affecting nearly two million persons in the United States alone. The incidence of RA in men under the age of forty-five is less than that reported in women, however the incidence approaches that of women in older age groups of men. This increased incidence in males coincides with decreasing levels of sex hormones. A hypogonadic condition characterized by low serum testosterone has been previously described in male RA patients compared with age-matched controls with osteoarthritis, ankylosing spondylitis and healthy controls. Patients with RA have significant disability with decreased function over time. Androgens have the potential to increase nitrogen retention, lean body mass, strength, and body weight which could slow the decline in function. Patients with RA also have both local and systemic forms of osteoporosis. There is evidence that androgens may stimulate the proliferation and differentiation of osteoblasts and osteoblast-like cells in vitro which may help reduce the rate of bone loss in RA. Previous studies in both animal models and humans seem to suggest that androgen administration may be beneficial in a number of autoimmune diseases including RA. In this study, we will examine the role of transdermal testosterone versus placebo in male patients with RA over a two-year period. Specifically, we will examine (1) the effect of testosterone on lean body mass and muscle strength with the use of whole body dual xray absorptiometry (DXA) scan and muscle strength testing, (2) the effect of testosterone on bone mineral density by DXA scan of the spine and hip, and (3) the effect of testosterone on disease specific measures of quality of life with validated instruments for quality of life. Additionally, measure of disease activity and side effects will also be assessed. The results of this study will (1) help to define the role of androgen administration and its effects on function through assessment of muscle mass and strength, (2) explore the potential benefits of testosterone therapy on bone mineral density in patients with both localized and systemic forms of osteoporosis, (3) define changes in quality of life in patients with RA treated with androgen, and (4) help to define the potential role of androgen therapy in other systemic illnesses where muscle wasting has a profound impact on quality of life (e.g. both inflammatory and non-inflammatory muscle disease). In addition, this K-23 grant will provide opportunity for further career development through mentorship provided by an committee with multiple areas of expertise and formal education in the areas of clinical research design and conduct, outcome assessment development and analysis, and clinical trial analysis.
AR027065	KHOSLA, SUNDEEP	EPIDEMIOLOGY OF AGE RELATED BONE LOSS AND FRACTURES	MAYO CLINIC ROCHESTER	This application is for renewed funding for yrs 21 to 25 of RO1 AR27065 "Epidemiology of Age-Related Bone Loss and Fractures." Osteoporosis accounts for at least 1.5 million fractures and costs $14 billion annually in the United States. We will continue our population-based studies on risk factors for osteoporosis using conventional methodologies and the infrastructure of the Rochester Epidemiology Project. However, we will also employ, for the first time in an epidemiologic study, two new state- of-the-art technologies--spiral volumetric quantitative computed tomography (QCT) of the spine and hips (CV 0.7-0.9%) and ultra-high resolution, 3-dimensional peripheral QCT (CV equal to or < 0.4%) of the distal radius and tibia. These instruments allow quantitative measurement of bone macrostructure, such as shape and size, separate determination of cancellous and cortical volumetric bone mineral density (BMD), and assessment of bone microstructural characteristics, such as cortical porosity and trabecular connectivity ("noninvasive bone biopsy"). The proposed research will extend followup on two age-stratified cohorts of Rochester, MN residents (304 **women** enrolled approximately 1980 and 351 **women** and 348 men enrolled approximately 1990) but most studies will be made in a new age-stratified cohort of 350 Rochester **women** and 350 men. Our Specific Aims are: 1) to validate a nationally-employed fracture prediction model; 2) to define the age-related, sex-specific changes of bone macro- and microstructure and to use these to test a number of hypotheses related to pathophysiology and to clinical issues; 3) to test the hypotheses that specific measurements of bone macrostructural and microstructural variables will greatly enhance fracture prediction as compared with BMD by dual-energy x-ray absorptiometry; 4) to assess the pathophysiologic mechanisms by which estrogen (E)-deficiency causes bone loss by testing the hypotheses that postmenopausal **women** with lower levels of E and E-metabolites have greater bone loss, that secondary hyperparathyroidism in late postmenopausal **women** interacts with E deficiency to protect against cancellous bone loss but to enhance cortical bone loss, and that alterations in levels of serum l,25(OH)2D3 and IGF-I contribute to bone loss in E deficient **women**; and 5) in **aging** men, to test the hypotheses that E-deficiency is the main cause of calcellous bone loss and T- deficiency is the main cause of cortical bone loss. The new bone structure measurements should take us to a new level of understanding of the causes of age-related bone loss and fractures and improve substantially the assessment of risk for osteoporosis.

rant Number	PI Name	Project Title	Institution	Abstract
AR035582	CAULEY, JANE A	OSTEOPOROTIC FRACTURES	UNIVERSITY OF PITTSBURGH AT PITTSBURGH	The Study of Osteoporotic Fractures (SOF) is a community-based prospective study in a cohort of 9,704 older women. SOF has comprehensive data about osteoporosis risk factors, along with an archive of serum, bully coat and urine specimens. Data from SOF have served for: (1) developing osteoporosis guidelines, (2) estimating the cost-effectiveness of screening for osteoporosis, and (3) planning trials of osteoporosis therapies. We propose to renew SOF to sustain this unique resource and to pursue several new hypotheses. Our preliminary findings suggest that BMD may lose predictive value for hip fractures after 4-5 years. We will study the long-term predictive value of BMD, and other risk factors, after 10-15 years; substantial declines would strongly effect guidelines concerning the frequency and cost-effectiveness of screening. We recently discovered that women with osteoporosis have a decreased risk of breast cancer, suggesting that these conditions share common etiologies. We will begin the search for these links by investigating whether endogenous sex steroids are associated with breast cancer, and whether other indices of osteoporosis, such as height loss, low ultrasound values, or incident fractures, indicate a lower risk of breast cancer. We have found that, contrary to previous beliefs, the rate of bone loss increases with age in Caucasian and African-American women. Elderly women also lose muscle mass as they age. We have also shown that mild chronic metabolic acidosis of dietary origin affects bone and causes negative nitrogen balance. We propose to test whether diet-induced metabolic acidosis, amplified by the normal age-related decline in renal function, is an important cause of loss of bone and muscle mass in elderly women, and is a risk factor for hip fracture. Declines in visual functions, such as contrast sensitivity, increase the risk of hip, wrist and humerus fractures and falls. Uncorrected refractive error and specific eye diseases, such as cataracts, glaucoma, and age-related macular degeneration, are common in elderly women. We will test the hypothesis that these common and potentially treatable eye diseases increase fall and fracture risk. Besides their scientific value, these findings may influence clinical guidelines and Medicare coverage for preventive eye care. Finally, there are contradictory findings about the relationship between estrogen receptor (ER) genotypes and bone mass and breast cancer, or even if ER variations have any biological effects. We propose using our archived DNA specimens and existing data about hip and vertebral fractures, breast cancer, bone mass, serum sex hormones and lipoproteins to determine whether these ER variations have biological importance.
AR035583	HARRIS, EMILY L	OSTEOPOROTIC FRACTURES (SOF)	KAISER FOUNDATION RESEARCH INSTITUTE	The Study of Osteoporotic Fractures (SOF) is a community-based prospective study in a cohort of 9,704 older women. SOF has comprehensive data about osteoporosis risk factors, along with an archive of serum, bully coat and urine specimens. Data from SOF have served for: (1) developing osteoporosis guidelines, (2) estimating the cost-effectiveness of screening for osteoporosis, and (3) planning trials of osteoporosis therapies. We propose to renew SOF to sustain this unique resource and to pursue several new hypotheses. Our preliminary findings suggest that BMD may lose predictive value for hip fractures after 4-5 years. We will study the long-term predictive value of BMD, and other risk factors, after 10-15 years; substantial declines would strongly effect guidelines concerning the frequency and cost-effectiveness of screening. We recently discovered that women with osteoporosis have a decreased risk of breast cancer, suggesting that these conditions share common etiologies. We will begin the search for these links by investigating whether endogenous sex steroids are associated with breast cancer, and whether other indices of osteoporosis, such as height loss, low ultrasound values, or incident fractures, indicate a lower risk of breast cancer. We have found that, contrary to previous beliefs, the rate of bone loss increases with age in Caucasian and African-American women. Elderly women also lose muscle mass as they age. We have also shown that mild chronic metabolic acidosis of dietary origin affects bone and causes negative nitrogen balance. We propose to test whether diet-induced metabolic acidosis, amplified by the normal age-related decline in renal function, is an important cause of loss of bone and muscle mass in elderly women, and is a risk factor for hip fracture. Declines in visual functions, such as contrast sensitivity, increase the risk of hip, wrist and humerus fractures and falls. Uncorrected refractive error and specific eye diseases, such as cataracts, glaucoma, and age-related macular degeneration, are common in elderly women. We will test the hypothesis that these common and potentially treatable eye diseases increase fall and fracture risk. Besides their scientific value, these findings may influence clinical guidelines and Medicare coverage for preventive eye care. Finally, there are contradictory findings about the relationship between estrogen receptor (ER) genotypes and bone mass and breast cancer, or even if ER variations have any biological effects. We propose using our archived DNA specimens and existing data about hip and vertebral fractures, breast cancer, bone mass, serum sex hormones and lipoproteins to determine whether these ER variations have biological importance.

rant Number	PI Name	Project Title	Institution	Abstract
AR035584	HOCHBERG, MARC C	OSTEOPOROTIC FRACTURES	UNIVERSITY OF MARYLAND BALT PROF SCHOOL	The Study of Osteoporotic Fractures (SOF) is a community-based prospective study in a cohort of 9,704 older women. SOF has comprehensive data about osteoporosis risk factors, along with an archive of serum, bully coat and urine specimens. Data from SOF have served for: (1) developing osteoporosis guidelines, (2) estimating the cost-effectiveness of screening for osteoporosis, and (3) planning trials of osteoporosis therapies. We propose to renew SOF to sustain this unique resource and to pursue several new hypotheses. Our preliminary findings suggest that BMD may lose predictive value for hip fractures after 4-5 years. We will study the long-term predictive value of BMD, and other risk factors, after 10-15 years; substantial declines would strongly effect guidelines concerning the frequency and cost-effectiveness of screening. We recently discovered that women with osteoporosis have a decreased risk of breast cancer, suggesting that these conditions share common etiologies. We will begin the search for these links by investigating whether endogenous sex steroids are associated with breast cancer, and whether other indices of osteoporosis, such as height loss, low ultrasound values, or incident fractures, indicate a lower risk of breast cancer. We have found that, contrary to previous beliefs, the rate of bone loss increases with age in Caucasian and African-American women. Elderly women also lose muscle mass as they age. We have also shown that mild chronic metabolic acidosis of dietary origin affects bone and causes negative nitrogen balance. We propose to test whether diet-induced metabolic acidosis, amplified by the normal age-related decline in renal function, is an important cause of loss of bone and muscle mass in elderly women, and is a risk factor for hip fracture. Declines in visual functions, such as contrast sensitivity, increase the risk of hip, wrist and humerus fractures and falls. Uncorrected refractive error and specific eye diseases, such as cataracts, glaucoma, and age-related macular degeneration, are common in elderly women. We will test the hypothesis that these common and potentially treatable eye diseases increase fall and fracture risk. Besides their scientific value, these findings may influence clinical guidelines and Medicare coverage for preventive eye care. Finally, there are contradictory findings about the relationship between estrogen receptor (ER) genotypes and bone mass and breast cancer, or even if ER variations have any biological effects. We propose using our archived DNA specimens and existing data about hip and vertebral fractures, breast cancer, bone mass, serum sex hormones and lipoproteins to determine whether these ER variations have biological importance.
AR038933	GRONOWICZ, GLORIA	GLUCOCORTICOIDS AND OSTEOBLAST APOPTOSIS	UNIVERSITY OF CONNECTICUT SCH OF MED/DNT	Our objective is to understand the contribution of apoptosis in determining bone mass and skeletal structure, in particular if apoptosis of osteoblasts contributes to the decrease in bone mass found with high dose glucocorticoids. We have shown that glucocorticoids induce apoptosis and estrogen prevents glucocorticoid-induced apoptosis in osteoblasts in vivo and in vitro. Glucocorticoids were shown to decrease bcl-2 and up-regulate bax levels creating a dose-dependent decrease in the bcl-2/bax ratio that resulted in cell death. We propose to study the effect of bcl-2 overexpression on, osteoblasts responses to glucocorticoids in vitro by transfection of osteoblasts. The extent of bcl-2 expression, the rate of apoptosis and proliferation, and the expression of bone markers will be assayed. We will then determine if bcl-2 overexpression in vivo will prevent the glucocorticoid-induced decrease in bone mass. A transgenic mouse will be constructed that overexpresses bcl-2 targeted to osteoblasts by the 2.3 kDa promoter region of the Type I collagen gone (Co12.3Bc1-2) and its bone phenotype will be characterized. Then these mice and their wild-type litter mates will be treated with and without glucocorticoids. Static and dynamic histomorphometry will be performed along with assays for apoptosis. Our hypothesis is that bcl-2 overexpression will partially prevent glucocorticoid-induced osteopenia. The specific osteoblast functions that are protected from glucocorticoids action in the Co12.3Bc1-2 mouse, will be studied. Finally, we will determine the time course and extent of apoptosis in bone cells after ovariectomy in wild-type and Co12.3Bc1-2 transgenic mice. Bone mass and apoptosis will be assessed. Since little is known about the role of apoptosis in determining skeletal structure and mass, these studies will test the hypothesis that systemic hormones, such as glucocorticoids, affect bone cell function and ultimately bone mass through the regulation of programmed cell death. We also seek to elucidate the contribution of apoptosis to glucocorticoid-induced osteoporosis. If apoptosis is an important determinant of bone mass, then our long-range goal is to develop novel strategies to prolong osteoblast survival and function during glucocorticoid therapy, and after **menopause** in patients at risk for osteoporosis.
AR039191	LINDSAY, ROBERT	SPECIALIZED CENTER OF RESEARCH IN OSTEOPOROSIS	HELEN HAYES HOSPITAL	Osteoporosis is recognized has a major public health problem in the USA today, with the likelihood of increased societal impact as "baby boomers" age. Therapeutic options are currently limited to "anti-resorptive" therapies which reduce bone turnover. Therapeutic options are currently limited to "anti-resorptive" therapies which reduce bone turnover, stabilize bone mass and reduce but not eliminate fracture risk, in part because many treated individuals are left with a bone mass that remains less than optimal. Thus, there is a clear need for agents that stimulate new bone formation. Our Specialized Center of Research has assembled a panoply of basic and clinical scientists to focus on this issue. Over the past 9 years we have investigated interactions of parathyroid hormone and sex steroids in the development and treatment of osteoporosis. Our cohesive and integrated approach has generated a significant base of knowledge, culminating in the demonstration that PTH (superimposed on standard HRT) not only increases bone mass but may also reduce vertebral fracture risk. In our current application, in four inter-related and integrated projects, we will examine aspects of PTH action at both basic and clinical levels. In Project 1 we will use novel techniques to isolate functional human osteoclasts and transgenic murine models to examine the mechanisms underlying osteoclast differentiation and death. In Project 2 the ovariectomized rat model will be used to evaluate morphological, biochemical, and mechanical responses to PTH, comparing a model of primary hyperparathyroidism (continuous PTH infusion) with intermittent PTH administration, in both estrogen replete and depleted states. The next project uses the paradigm of endogenous primary hyperparathyroidism in post-menopausal women to characterize the effects of chronically increased PTH, and its reduction (after parathyroidectomy) on skeletal homeostasis. The last project focusses on the mechanism underlying the initial period of new bone formation that occurs in the early months of PTH therapy, as well as the effects of withdrawal of treatment. Each of these projects relies heavily on the support of "Core" units,: Administration/Statistics; Biochemistry; Histomorphometry; and Bone Mass Measurement, with integration of all Projects and Cores with regard to protocols, investigators and data interpretation.

rant Number	PI Name	Project Title	Institution	Abstract
AR039191	IIDA-KLEIN, AKIKO	ANABOLIC AND CATABOLIC ACTIONS OF PTH IN ANIMAL MODELS OF ESTROGEN DEFICIENCY	HELEN HAYES HOSPITAL	Osteoporosis has become a major health problem as the life expectancy of the general population has risen rapidly in recent years. Post-menopausal **women** are at greater risk because of accelerated bone loss induced by estrogen deficiency superimposed on age related bone loss. One of the important etiological factors in postmenopausal osteoporosis is the interaction between estrogen and PTH. PTH is known to be an important initiator of bone remodeling and persistent elevation of PTH, such as in hyperparathyroidism, presents as a risk factor for the development of osteoporosis. However, intermittent administration of PTH has been shown to be a promising regimen for improve bone mass in both the animals and humans. The dichotomy of this issue is not fully understood, especially in the estrogen deficient population. This project attempts to understand further the dualistic role of PTH as a catabolic and anabolic **hormone** in animal models of estrogen deficiency. The proposed study will have the following specific aims. Specific Aim 1. To differentiate the anabolic action of continuous elevation of PTH from its catabolic action. Specific Aim 2. To demonstrate the interactions of dietary calcium intakes with continuous and intermittent PTH administration under estrogen deficiency state, and Specific Aim 3. To study the interactions of PTH, cytokines and anti-resorptive agents at both tissue and subcellular levels in a mouse model of estrogen deficiency.
AR039191	BILEZIKIAN, JOHN	THE EFFECT OF PRIMARY HYPERPARATHYROIDISM ON THE BONES OF POSTMENOPAUSAL WOMEN	HELEN HAYES HOSPITAL	In the renewal period this Project will investigate the mechanisms of bone loss through the paradigm of primary hyperparathyroidism in estrogen deficient, postmenopausal subjects. The studies are based upon observations we have made in the previous funding period. Cancellous bone is preserved while cortical bone is at risk. Postoperatively, there is a pervasive gain in bone mass at all sites, irrespective of their composition type. In the renewal period, these central observations will be pursued further with attention to four specific areas. We will continue to monitor the course and reversibility of the hyperparathyroid process in postmenopausal **women**. These studies will include a longitudinal analysis utilizing serum and urinary biochemical determinations, densitometry, and histomorphometry. Second, we have identified subgroups of postmenopausal **women** who may be at risk for deleterious outcomes. Three groups have been identified: **women** who present in an anomalous fashion with reduced cancellous bone content perimenopausal **women** whose hyperparathyroidism is potentially adversely influenced by the onset of estrogen deficiency; and **women** who are deficient in vitamin D. A third area of inquiry is a characterization of biochemical mediators of parathyroid **hormone** action as they related to other indices of disease activity, to pathophysiological consequences, and to postoperative recovery. The fourth area to be studied in Project 4 is the histomorphometric features of bone in primary hyperparathyroidism. We plan to reconstruct the dynamics of the bone remodeling unit in primary hyperparathyroidism. We plan to reconstruct the dynamics of the bone remodeling unit in primary hyperparathyroidism. We will also be assessing the histomorphometric changes that occur after patients undergo successful parathyroid surgery in an attempt to understand the counter-intuitive robust increase in bone mass that follows. Bone biopsy samples will be obtained before and one-year postoperatively. Along with detailed biochemical and densitometric studies that will be conducted over this same period, we should be uniquely poised to gain more complete understanding of the anabolic and catabolic properties of parathyroid **hormone**. The project melds with the overall aim of the SCOR in that it should lead to additional insight into mechanisms of bone loss in general among postmenopausal **women** and how these mechanisms, presumable due to estrogen deficiency, are influenced by parathyroid **hormone**.
AR041325	BOSKEY, ADELE	FT-IR MICROSCOPY OF MINERAL STRUCTURE IN OSTEOPOROSIS	HOSPITAL FOR SPECIAL SURGERY	Osteoporosis is estimated to affect 15-20 million people (both **women** and men) each year, causing significant morbidity and mortality. The widely used predictors of fracture risk are bone mineral density (BMD) and incidence of a previous fracture. One of the dilemmas in the management of osteoporosis is that two individuals with the same bone density and similar life-styles can show extensive diversity in their tendency to fracture. There is little information on what, other than differences in life style and fall severity, can account for this discrepancy. The underlying hypothesis of this grant is that discrete differences in mineral and matrix properties contribute to the altered fracture risk in these individuals. Over the past two funding periods, we have shown that Fourier transform infrared microspectroscopy (FTIRM) and imaging (FTIRI) provide reproducible and valuable information on the mineral and matrix properties of bone. We now wish to extend this approach to two new research questions: Aim 1) Do the mineral and matrix properties differ in biopsies from patients with fracture compared with patients without fractures while controlling for age, gender, bone mineral density, and architecture? This question will be tested by assessing biopsied specimens from individuals with different fracture histories and with known age, gender, and bone mineral density. MicroCT will be used to assess architecture of the specimens, and FTIR will be used to characterize mineral and matrix properties. Under this specific aim, we will also examine associations between FTIR parameters and nanoindentation in a subset of biopsies to establish the nanoindentation technique and to test for significant correlations between mineral/matrix properties and indentation modulus and hardness. We will also develop the use of imaging ATR to establish an IR approach that does not required thin sections of embedded bone. Aim 2) Do therapeutic agents reverse the observed alterations in mineral and matrix properties? Specifically we shall examine the relative effects of a SERM (selective estrogen receptor modulator), raloxifene, **Hormone** Replacement **Therapy**, and a bisphosphonate (Risedronate) on the mineral and matrix properties in pre- and post- **therapy** biopsies, to identify the agent(s) that reverse(s) the observed alterations in mineral and matrix properties. Emphasis will be placed on those properties identified in Aim 1 that are most predictive of fracture.

rant Number	PI Name	Project Title	Institution	Abstract
AR041398	KIEL, DOUGLAS P.	RISK FACTORS FOR AGED RELATED BONE LOSS	HEBREW REHABILITATION CENTER FOR AGED	Osteoporosis and related fractures represent major public health problems that will only increase in importance as the population ages. Several studies have now convincingly demonstrated that aging-related bone loss continues, and may even accelerate, in extreme old age. A better understanding of the factors that may be unique to bone loss in old age may help to refine the types of interventions to preserve bone mass in old age. The present application is a competing continuation proposal from the Framingham osteoporosis study group to examine in detail several risk factors for bone loss in old age using three related cohorts, the original Framingham cohort, The Framingham Offspring cohort and a new Framingham minority cohort. The Original Framingham cohort has been the subject of two previous exams that included measurement of bone density. The Framingham Offspring Cohort was recruited from among the children, and their spouses, of members of the original cohort starting in 1971; 3570 are expected to participate in this osteoporosis study. The Minority cohort is currently being recruited and will consist of 300 subjects (34% black and 66% Hispanic). The proposed studies will extend and expand upon the research group s previous investigations of more traditional risk factors for bone loss by taking advantage of developments in nutritional assessment, as well as findings from cellular and molecular biology of bone, which offer an opportunity to examine risk factors for bone loss that have been less well studied. The primary aim (1) of the proposed studies is to examine the effect of dietary factors on bone health, in particular the effect on bone density and bone loss of consumption choices among common food groups, and the effect on bone loss of specific nutrients that have not been well-studied with regard to bone, including magnesium, potassium, vitamin C, sodium, and vitamin K. The dietary studies will be performed using longitudinal data on bone density from the original Framingham cohort, and using cross-sectional bone density data in the Offspring and Minority Cohorts. Dietary data, in the form of food frequency questionnaires in all three cohorts, and 3 day food records in the Offspring Cohort, have already been collected at previous examinations. For this aim, follow-up for bone loss in the Original Framingham Cohort will be extended from 4-5 years to 8 years by adding an assessment of bone density at a planned future Framingham biennial examination (Exam 24). A special call back visit will be required to obtain bone density in all of the approximately 3,600 members of the Offspring Cohort. Both dietary data and bone density are already being measured in an ongoing examination of the Minority Cohort. There are also several other Aims of the study, as follow: (2) to examine the cross-sectional association of IGF-1 and IGF-BP4 with bone density in a subset of 100 men and 100 women in the Framingham Offspring cohort using blood specimens obtained 5 years prior to the measurement of bone density; (3) to examine the cross-sectional association with bone density of two new measures of weight-bearing physical activity, a validated questionnaire and an automated weight-bearing activity monitor, in subsets of 200 men and 200 women in each of the Original and Offspring Cohorts; physical activity will also be examined in relation to a new measurement of QUS of the heel in this subset from the Original cohort; the physical activity measures will be obtained in a special callback or regular visit in the Offspring Cohort and at Exam 24 in the original cohort; and (4) to compare measures of quantitative ultrasound (QUS) of the calcaneus between members of the Original Cohort who attend Exam 24 and those who are unable to attend the exam to determine if bone loss may be underestimated by studying subjects who attend clinic examinations. QUS will be assessed with a new dry system device in all those in the original cohort who attend Exam 24 as well as those who receive the standard Framingham home visit.
AR041443	WEHRLI, FELIX W.	NMR IMAGING AND STEREOLOGIC ANALYSIS OF TRABECULAR BONE	UNIVERSITY OF PENNSYLVANIA	Most osteoporotic fractures occur at skeletal locations rich in cancellous (trabecular) bone. The most widely used criterion for risk assessment is bone mineral density (BMD). However, it is well known that BMD is not a satisfactory predictor of fracture risk. Indeed, there is now compelling theoretical, experimental and clinical evidence for the role of architecture as an additional predictor of the bone's mechanical competence. During the past cycles of this project we have shown both in the laboratory and in patient studies that magnetic resonance micro-imaging (mu-MRI), in conjunction with image analysis, can predict the trabecular bone's mechanical behavior and clinical outcome, respectively. In preliminary work we have conceived a new approach toward a complete quantification of cancellous bone architecture based on three-dimensional digital topological analysis and have shown that this techniques accurately describes the conversion of trabecular plates to rods, a process well known to occur during aging and, in particular, in osteoporosis. Paralleling these developments we have made significant progress in data acquisition, processing and analysis, which improved both sensitivity and precision of mu-MRI to the extent that longitudinal studies are now feasible. During the next phase of the project we propose (i) to further develop and evaluate digital topological analysis and additional structural analysis tools; (ii) to determine the precision of the mu-MRI-derived topological and scale parameters in specimens and representative patients; (iii) to assess the sensitivity of the method to detect linearchitectural changes during early menopause in a pilot project involving women treated with estrogen and their controls; (iv) to compare sensitivity and precision of mu-MRI with DEXA and p-QCT. The overall hypothesis to be tested is that mu-MRI-based cancellous bone structural analysis is sensitive and reproducible and capable of detecting changes in cancellous bone architecture as they occur over time, either as a result of normal changes or in response to treatment. The long-term goal of the work proposed is to establish "virtual bone biopsy," analogous to physical bone biopsy, by three-dimensional architectural analysis of mu-MRI data collected in vivo, as a means to follow patients longitudinally, either as a method for assessing osteoporosis risk or for evaluating treatment efficacy.

rant Number	PI Name	Project Title	Institution	Abstract
AR042540	BUYON, JILL P.	SAFETY OF ESTROGEN IN LUPUS ERYTHEMATOSUS-NAT'L ASSESS'	HOSPITAL FOR JOINT DISEASES ORTHO INST	The current proposal addresses the effect of exogenous female hormones on disease activity and severity in women with systemic lupus erythematosus (SLE). Oral contraceptives (OCs) and estrogen replacement therapy (ERT) are generally not prescribed due to the widely-held view that they can activate SLE. This practice is based on the greater incidence of SLE in women than in men, biologic abnormalities of estrogen metabolism, murine models of lupus, several anecdotes of patients having disease flares while receiving exogenous hormones, and a single retrospective study in patients with pre-existing renal disease. In contrast, recent retrospective studies suggest that the rate of flare is not significantly increased in patients taking OCs or ERT. The pre- existing data are insufficient to warrant the dismissal of a potentially important birth control option in a disease which predominantly affects women in their reproductive years and whose fertility is not altered by the disease. Moreover, the use of OCs to preserve fertility in patients taking cyclophosphamide, and the use of estrogens to prevent coronary artery disease and postmenopausal and steroid-induced osteoporosis are timely considerations. In Specific Aim 1 we will attempt to define, in a randomized double-blind placebo-controlled trial, the effect of OCs containing low dose synthetic estrogens and progestins on disease activity in women with SLE. Since the research hypothesis is that OCs do not increase the risk of flares, the study has been designed to be able to detect minimal increases in the rate of flares in patients taking OCs. Patients with \pard softlineinactive, stable or moderate disease requiring less than 0.5 mg prednisone per kg of bodyweight per day will be enrolled over a 2-year period and randomized to receive triphasic ethinylestradiol/ norethindrone or placebo for 12 months. In Specific Aim 2, we will) examine, in a randomized double-blind placebo-controlled trial, the effect of hormonal replacement with conjugated estrogens and cyclic low- dose medroxyprogesterone acetate on disease activity in postmenopausal women with SLE. Patients will be enrolled over 3 years and receive hormones for 1 year. This multicenter study represents a first-time clinical research collaboration between 5 major rheumatology centers: Hospital for Joint Diseases/Bellevue Hospital/New York University, Hospital for Special Surgery/Cornell University Medical, St. Luke's/Roosevelt Hospital Center, The Johns Hopkins Medical Center, and UCLA School of Medicine/LA County Harbor Medical Center. Patients will be recruited from the clinics and private practices which include over 4,000 women with SLE, most belonging to minority groups. The proposal embraces the cooperative efforts of rheumatology, reproductive endocrinology, epidemiology, and biostatistics, to initiate needed prospective controlled studies. Such approaches have already changed long-held beliefs about the risk of lupus flares during pregnancy.
AR042739	GIGER, MARYELLEN L.	COMPUTERIZED RADIOGRAPHIC ANALYSIS OF BONE STRUCTURE	UNIVERSITY OF CHICAGO	This abstract is not available.
AR042906	BROOKS, GEORGE	EXERCISE SUBSTRATE UTILIZATION: THE CROSSOVER CONCEPT	UNIVERSITY OF CALIFORNIA BERKELEY	Our overall objective is to identify and understand the factors that control the balance of energy derived from endogenous carbohydrate, lipid, and amino acid sources during sustained, submaximal exercise. A related objective is to understand how various life situations (physical fitness, diet, gender, age) affect the balance of substrate utilization (partitioning) in humans. The theoretical basis of our approach is the 'Crossover Concept' which postulates that during rest and mild to moderate intensity exercise in the post-absorptive state, lipids provide the greatest proportion of energy for muscle and the body at large. However, as the exercise intensity increases from moderate to hard to maximal, the balance of substrate utilization in working muscle switches, or 'crosses over' from lipid to carbohydrate. Using this concept, we seek to describe the mechanisms by which exercise, exercise training, ovarian steroids, age, and dietary history affect the balance of substrate utilization. In pursuit of our overall objective, we propose to explore two specific aims. These are to: (1) describe the interactive effects of exercise intensity and endurance training on muscle and whole body fatty acid oxidation; and (2) evaluate the effects of aging and ovarian sex steroids on the balance of substrate utilization. With these data we shall be able to expand our model of substrate utilization. To assess effects of exercise intensity and to make comparisons at given relative and absolute exercise intensities before and after endurance training, for Aim 1 young men will be studied before training at power outputs (P0) that elicit 45 and 65% VO2peak; after training they will be studied at the P0 that elicited 65%V02peak before training, and at the new 65%V02 peak. To assess acute and long-term metabolic and enzymatic responses at whole-body and working muscle (leg) levels we will use the combination of tracers {[1-13C]palmitate, [1,1,2,3,3-2H2]-glycerol (D5-glycerol), and D2-glucose}, indirect calorimetry, (a-v) measurements, biopsies, and, possibly, NMR spectroscopy. For Aim 2 studies on older men, young amenorrhic as well as older postmenopausal **women** we will use tracers {[1-13C]palmitate, D5-glycerol, D2- and [1-13C]glucose, as well as [1-13C]leucine}, and indirect calorimetry. On older **women** longitudinal designs will be employed to assess effects of training and HRT on substrate partitioning. Age-matched males will also be studied. All techniques, whether they involve exercise physiology, indirect calorimetry, tracer infusion and blood sampling, metabolite derivatization, isotopic enrichment determination by GC /MS, metabolite and **hormone** assays, Western blotting and dietary control, are highly developed by the investigative team. Further, we have the auxiliary personnel and facilities to conduct longitudinal training studies

rant Number	PI Name	Project Title	Institution	Abstract
AR043510	BOYCE, BRENDAN	STUDIES OF THE FATE OF THE OSTEOCLAST	UNIVERSITY OF ROCHESTER	Osteoclasts are required for the normal development of bone during endochondral osification and for the resorption of worn-out bone in the adult skeleton during normal bone remodeling. They also mediate the increased bone loss that occurs in association with inflammation in bone and estrogen deficiency following **menopause**. Recent studies indicate that expression of M-CSF and RANK (receptor activation of NF-kappaB) ligand is required for osteoclast formation and that activation of genes regulated by the transcription factors, c-fos, PU.1 and NF-kappaB is also necessary. NF-kappaB regulates the expression of the osteoclastogenic cytokines, IL-6, IL-1, and TNF whose expression is up-regulated in inflammatory bone diseases and in response to estrogen deficiency. These cytokines also prevent osteoclast apoptosis, and the increased bone resorption seen after the **menopause** may in part be due to prolongation of osteoclast life spans on bone surfaces. NF-kappaB has also been shown to prevent TNF- and FAS ligand-induced apoptosis of some cell types and therefore may be involved in the regulation of osteoclast life span. Thus, NF-kappaB may regulate not only the formation of osteoclasts in normal bone remodeling, but also the increased production and prolonged life spans after the **menopause**. However, the molecular mechanisms whereby NF-kappaB mediates these activities in osteoclasts in osteoclasts are largely unknown and are likely to involve multiple signaling pathways in osteoclasts and their precursors and osteoblasts. We propose to use a combination of in vitro and in vitro approaches to study the role of NF- kappaB in osteoclast formation, activity and survival. Our specific aims are to determine the role of NF-kappaB in 1) osteoclast formation 2) the up- regulation of osteoclastogenesis induced by cytokines and estrogen deficiency and 3) the regulation of osteoclast apoptosis Our underlying hypothesis is that NF-kappaB is required for the activation of genes encoding cytokines which are essential for 1) the progression of osteoclast precursors along a differentiation pathway to form mature osteoclasts; 2) the up-regulation of osteoclastogenesis following estrogen withdrawal; and 3) for the survival of osteoclasts by preventing them from undergoing apoptosis. Understanding the role of NF-kappaB in osteoclastogenesis and survival could lead to the development of new therapeutic agents designed specifically to inhibit bone resorption in conditions, such as postmenopausal osteoporosis, in which it is increased.
AR043618	BEAMER, WESLEY G.	GENETIC AND DYNAMIC ANALYSES OF PEAK BONE DENSITY	JACKSON LABORATORY	Osteoporosis is a bone wasting disease that afflicts about 20 million Americans. Osteoporotic fractures occur when bone density (BD) falls below the fracture threshold, a change dependent upon the peak bone density achieved by young adulthood and the subsequent net bone loss after the menopause. Up to 70% of the variation in peak BD within is inheritable. Recognizing that it is important to identify genes responsible for peak BD, the applicants initiated studies in genetically-defined inbred strains of mice. This led to discovery of a genetic model with two inbred mouse strains, C57BL/6J and C3H/HeJ, with highly significant differences in vertebral (11%), tibial (34%), and femoral (54%) BD. By using a combination of pQCT, serum and urine biochemical assays of bone formation (BF) and bone resorption (BR), and histomorphometry, they have obtained the following preliminary data. The C3H/HeJ mice (highest BD) differed from the C57BL/6J mice in the following manners: 1) reduced medullary cavity volume and increased cortical thickness; 2) increased metaphyseal trabecular BD, indicating interstrain differences occur at the endosteum and at trabecular bone: 3) decreased serum osteocalcin, serum skeletal alkaline phosphatase, and urine crosslinks/creatinine at 2 months of age; and 4) decreased osteoclast number at both endosteal cortex and trabecular bone at 2 months of age, suggesting that at this time point, decreased BR contributed to the interstrain difference in BD. Based on this preliminary data, they have advanced two hypotheses: 1) the interstrain difference in BD is determined by a fixed number of genes that can be mapped; and 2) the interstrain difference in BD is a consequence of gene effects on endosteal/trabecular BF or endosteal/trabecular BR, or both. To test the first hypothesis, a combination of genetic crosses and molecular analytic approaches will be applied to: 1) intercross F2 progeny for quantitative trait loci analyses (QTL) with the C57BL/6J and C3H/HeJ strains, plus recombinant inbred (RI) strain analyses using the BXH RI strain set derived from C57BL/6J and C3H/HeJ progenitors; and 2) recombinant congenic (RC) strains plus backcrosses of RC strains with C57BL/6J. Correlation of BD phenotypes with segregating DNA polymorphisms will establish genetic linkage, estimate the number of genes involved with interstrain bone density differences, genetically order bone regulatory genes with major and important modifier effects, define mode of inheritance for each gene, and evaluate parent-of-origin effects on BD. To test the second hypothesis, longitudinal studies will be conducted during development of peak BD in the two inbred mouse strains, applying methodologies for BD, bone histomorphometry, and bone biochemical assays. The data obtained will be analyzed: 1) to quantitatively describe the BF and BR mechanisms that account for the increase in BD within each mouse strain; and 2) to determine the differences in BF and BR that account for the difference in peak BD between the mouse strains. Ultimately, the applicants propose to correlate the phenotypic modeling mechanisms disclosed by their dynamic studies of bone modeling with the genes mapped in the first Aim.
AR044655	BECK, THOMAS J.	STRUCTURAL ANALYSIS OF DEXA SCANS: OSTEOPOROSIS STUDIES	JOHNS HOPKINS UNIVERSITY	This abstract is not available.

rant Number	PI Name	Project Title	Institution	Abstract
AR044661	BOUXSEIN, MARY L.	ASSESS OSTEOPOROTIC FRACTURE RISK	BETH ISRAEL DEACONESS MEDICAL CENTER	Osteoporosis is a common condition that presently affects more than 25 million persons in the US, contributing to over 1.5 million fractures annually. The economic and social impact of these fractures on health care delivery and on the elderly population are staggering. Furthermore, if current trends continue, the number of fractures and associated costs are projected to double or triple in the next 30 years due to the aging of our population. Early identification, through widespread screening programs, and intervention in those persons at high risk may improve the success of fracture prevention strategies. The most commonly used technique for assessing fracture risk, dual-energy x-ray absorptiometry (DXA), though proven effective as a predictor of future fracture risk, may not be the ideal screening tool due to the relatively high capital investment required, the need for specialized operator training, and limited portability. Recently, alternatives to DXA have been developed. We propose studies designed to further our basic understanding and to evaluate the potential usefulness of two of these alternative methods: image analysis of conventional radiographs and quantitative ultrasound (QUS). In the first two aims we will evaluate a diagnostic technique based on image processing of conventional forearm radiographs. In this technique, a bone index representing the character of the projected trabecular pattern is computed from standard radiographs. We will compare this bone index to the strength of cadaveric femurs and thoracolumbar vertebrae, and assess its ability to predict hip fracture risk in case-control study of women with an acute hip fracture and similarly-aged women who have not suffered a fracture. In our final aim, we will examine the capabilities of QUS. It has been proposed that QUS measures aspects of bone "quality", such as trabecular architecture, material properties, or accumulated microdamage, that are independent of bone density. However there have been few studies relating QUS measurements on intact feet (rather than excised bone specimens) to aspects of bone quality. We will use human cadaveric specimens to characterize the relationship between QUS measurements of on intact feet and trabecular bone morphology, mechanical properties, and microdamage. The significance of the proposed work is that is will provide new information regarding the potential usefulness of two technologies that may be capable of widespread osteoporosis testing and assessment of fracture risk. This information is important, as early identification of those at risk for fracture represents the most promising approach for effective fracture prevention.
AR044855	NEER, ROBERT	ANABOLIC ACTIONS OF PTH IN OSTEOPOROTIC MEN AND WOMEN	MASSACHUSETTS GENERAL HOSPITAL	Once-daily PTH injections increase bone mass and strength more than other treatments in osteoporotic **women** and men, but rarely cure osteoporosis. Daily PTH injections increase bone resorption as well as formation, so combining them with an anti-resorptive agent should enhance the effect on bone mass. Experiments elsewhere in animals and humans failed to confirm this expectation, but their design made interpretation difficult, so we are treating osteoporotic **women** and men with PTH, alendronate, or both, serially assessing bone formation and resorption and BMD of multiple sites. This also tests whether PTH must increase bone resorption in order to increase bone formation and BMD in humans, or whether a bisphosphonate interferes with PTH-mediated increases in bone formation. At the end of this experiment we will evaluate skeletal and renal responses to sc PTH, and to a 12-hour iv PTH infusion, stop PTH but not alendronate, follow the patients for a year, and then re-evaluate BMD and acute responses to sc and iv PTH. This will test whether acute renal and early skeletal responses to PTH are restored by a 12 month interval without PTH administration, and whether BMD increases after stopping PTH (because bone remodeling decreases) or whether (as in animals) BMD decreases rapidly after stopping PTH, unless an anti-resorptive agent is administered. We will then treat every patient with PTH for a year (not changing any alendronate treatment), to test whether daily sc PTH's effects on bone turnover are restored by a 12 month interval without PTH administration, with additional increases in BMD. In osteoporotic animals and humans, PTH?s therapeutic effects are limited by a PTH resistance that slowly develops during prolonged daily PTH administration. We will test whether this PTH resistance reflects decreased blood levels of the injected peptide, delayed development of anti-PTH antibodies, down-regulation of PTH-receptors and receptor-mediated activation of adenylate cyclase (in an accessible PTH target organ, the kidney), or a decrease in PTH?s early effects on bone formation (the suppression of bone formation and stimulation of bone resorption seen during a 12-hour intravenous PTH infusion). Finally, we will test in a new set of patients whether PTH resistance can be overcome by serial increases in the administered PTH dose.
AR045222	FU, SHU	ESTROGEN RECEPTOR IN SLE	UNIVERSITY OF VIRGINIA, CHARLOTTESVILLE	Systemic lupus erythematosus (SLE) is a prototypic systemic autoimmune disease with gender-bias affecting mostly **women** of childbearing age. The basis of the gender bias remains to be elucidated. In this proposal, significant preliminary data to support the preferential expression of estrogen receptor (ER)b by T cells from SLE patients provide the basis to explore the role of interactions of estrogen and its receptors in the pathogenesis of SLE and its predilection for females. Three specific aims are proposed. Specific Aim 1 will examine the protein and mRNA expression of ERa and ERb in circulating T cells of patients with SLE in comparison with healthy Controls to establish that there is preferential expression of ERb by T cells isolated from SLE patients and to determine the basis for this preferential expression. Specific Aim 2 will determine if ER activation differs in T lymphocytes from SLE patients and controls and to determine whether altered sensitivity of T cells from SLE patients and certain normal control populations is due to the effects of proteins which regulate ER activity. Specific Aim 3 will compare ER function between the normal strains and autoimmune-prone strain NZM2328, and to generate ERa-/- and ERb-/- mutants in NZM2328 background and to phenotype these mutants for autoantibody production and the induction of acute and chronic glomerulonephritis. Under the direction of this project, the U.Va Lupus Cohort Database is maintained for the use by SCOR investigators. The results of these experiments will provide further insight into the mechanisms of sex **hormone** influence in autoimmunity and the basis for the gender-bias in this disorder. In addition, they might also provide the rationale for hormonal ablation as an adjunct **therapy** for SLE.

rant Number	PI Name	Project Title	Institution	Abstract
AR045233	TURNER, RUSSELL T.	ESTROGEN METABOLITES EFFECTS ON BONE	MAYO CLINIC ROCHESTER	A serious obstacle to the rational design of innovative approaches for preventing and/or treating osteoporosis is the idiopathic nature of postmenopausal bone loss. Menopause is the most important risk factor for osteoporosis. However, not all postmenopausal women develop osteoporotic fractures indicating that cessation of the menstrual cycle is insufficient to fully account for the disorder. Our working hypothesis is that the denovo production and metabolism of estrogens are among the most important factors influencing the rate of postmenopausal bone loss. Estrone (E1) and its metabolites, 16alpha-Hydroxyl estrone ((16alpha-OHE1) and 2-hydroxyesterone (2-OHE1), are the most abundant estrogens in postmenopausal women. 16alpha-OHE1 has been recently shown to be a negative risk factor (reduced risk) for postmenopausal bone loss, whereas 2-OHE1 has been positive risk factor (increased risk). 2-OHE1 does not have estrogenic activity in ovariectomized (OVX'd) rats. In contrast, 16alpha-OHE1 appears to be a tissue selective estrogen agonist with a profile of activity similar to the anti-breast drug tamoxifen; 16alpha-OHE1 is a much more effective estrogen agonist on bone and liver than on reproductive tissues. These observations suggest that differences in the skeletal activities on 2-OHE1 and 16-alpha-OHE1 are responsible for the observed association between bone mass and circulating levels of these metabolites in postmenopausal women. We propose to test this hypothesis in ovary intact and OVX'd rats. The specific aims are to determine the dose response effects of 2-OHE1 and 16alpha-OHE1 on the expression of immediate response genes in bone and other estrogen target tissues; and establish the long-term effects of the estrone metabolites on bone architecture, turnover and strength. The proposed research will characterize the probably cellular mechanisms of action. The results of these studies are likely to be relevant to women because of the similarity between postmenopausal bone loss and OVX-induced bone loss in rats, as well as the previous success the rat model has enjoyed for predicting the response of the human skeleton to estrogen agonists and markers to predict the rate of postmenopausal bone loss; 2) manipulation of estrone metabolism by changes in diet or by pharmacological intervention may be a valuable tool for reducing bone loss; and 3) analogs of 16alpha-OHE1 may be useful for prevention and treatment of postmenopausal osteoporosis.
AR045713	LANG, THOMAS	PRECISE 3D QCT TO MONITOR OSTEOPOROSIS THERAPY	IMAGE ANALYSIS, INC.	The growing number of **women** receiving drug treatment for osteoporosis underscores the need for sensitive methods to monitor **therapy**. Because it permits selective assessment of the trabecular and cortical bone, which may respond differently to disease and **therapy**, quantitative computed tomography (QCT) is well-suited to this purpose. However, the ability of QCT to resolve **therapy**- or disease-induced changes in bone mineral density (BMD) is limited by variable precision errors. These precision errors mostly relate to the operator-dependence of current techniques, which involve manual slice selection and region of interest placement. In our Phase I Grant, we have addressed this problem by developing and demonstrating the feasibility of an image registration algorithm which aligns serial images and uses the resulting 3D transformation to map a baseline region into the same volume of the follow-up image. As we have documented in the Phase I Final Report, this fast and automated approach yields precision errors in vivo of 1.0 mg/cc and 0.9 mg/cc for spinal and proximal femoral trabecular BMD measurements respectively. In this application, we propose to develop and commercialize a prototype software package which will combine diagnostic 3D QCT BMD measurements with our new approach for highly reproducible longitidunal measurements. PROPOSED COMMERCIAL APPLICATION: We will provide commercial CT imaging centers with a powerful set of tools which they can use to compete in the bone mineral density measurement market. The diagnostic measurement component will allow CT scanners to measure bone mineral density in the spine and hip in bone regions comparable to those measured by DXA. Moreover, the high reproducibility of our technique will permit CT centers to offer a method for monitoring **therapy** effects which will be superior to DXA.
AR045734	DAWSON-HUGHES, BESS V	NIH OSTEOPOROSIS & RELATED BONE DISEASES RESOURCE CENTER	NATIONAL OSTEOPOROSIS FOUNDATION	This abstract is not available.
AR046032	NAFTOLIN, FREDERICK	AROMATASE INHIBITOR METHYL TESTOSTERONE AND TESTOSTERONE INDUCED BONE SPARING	YALE UNIVERSITY	Osteoporosis is a common disease in postmenopausal **women** and aging men resulting in considerably morbidity and mortality. While estrogen is a recognized bone-sparing agent, reports on the effect of testosterone (T) on bone mass are controversial and variable. T's variable action on bones could be due to the requirement of aromatization of T to estrogen, followed by action on bone cell estrogen receptors: This laboratory was first to report the presence of immunoreactive aromatase in osteoblasts in culture. 17alpha-methyl testosterone (MT) is a synthetic steroidal androgen with low affinity for the androgen receptor. It is widely used in **hormone** replacement **therapy** in **women**. MT is also a powerful aromatase (estrogen synthetase) inhibitor that may block local estrogen formation. We have shown that MT inhibits both aromatization of androstenedione and T-induced proliferation of breast cancer cells by inhibiting aromatase. We propose to use a similar preclinical experimental approach to assess the mechanism of action of T on rat bone mass: We will test the effect of T alone and of T plus MT on bone maintenance in ovariectomized female rats. If MT blocks T's bone maintenance, this will indicate that T's action is indirect, via aromatization, and justify clinical studies.

rant Number	PI Name	Project Title	Institution	Abstract
AR046859	PREVRHAL, SVEN	MEASUREMENT OF THICKNESS/DENSITY OF THE PROXIMAL FEMUR	UNIVERSITY OF CALIFORNIA SAN FRANCISCO	Hip fracture is one of the most severe implication of Osteoporosis, a disease affecting millions of elderly people world-wide. The clinically established method to predict a person's hip fracture risk, bone densitometry, cannot separately measure the status of trabecular and cortical bone but only reports overall bone density. There is evidence that both compartments individually contribute to bone strength but are differently affected by aging or osteoporotic changes and therapeutic regimens. This research effort will approach the following questions: Can the density and the thickness of cortical bone in the proximal femur be measured accurately with volumetric Quantitative Computed Tomography (vQCT)? Does the knowledge of these parameters aid in predicting mechanical integrity in addition to standard bone densitometry? To what extent is the technique applicable in vivo? To assess the accuracy of vQCT, a comparison to Micro-CT is planned. Micro-CT is a Computed Tomography technique on microscopic level (the spatial resolution is 25 mm for the instrument being used) and has recently been extended to scan whole proximal femora. It can therefore be used as a gold standard to evaluate vQCT. Out of a total of 25 excised cadaveric proximal femora from elderly women who did not have diseases known to affect bone, 5 will be scanned with vQCT and Micro-CT. The analysis tools, which will comprise segmentation of the cortical wall and local measurement of cortical bone mineral density and thickness, will be applied to both data sets. The other 20 specimens will be subjected to vQCT, standard bone densitometry and mechanical testing. During the latter, bone elasticity and ultimate failure load will be recorded. The gathered data will allow to estimate the relative contribution of the cortical thickness and density to mechanical integrity and to locate the most sensitive regions of the cortex. The question of whether a vQCT scan of cortical bone can add information to standard bone densitometry can also be answered. The third part of the study will focus on clinical feasibility of vQCT of cortical bone. Its specific aim is reducing the radiation exposure by limiting the CT scan volume and decreasing the amount of radiation used. By analyzing the impact of the consequential increase of image noise and loss of spatial resolution on the measurability of cortical density and thickness optimal CT imaging parameters will be derived.
AR046922	ALEKEL, LEE D	BONE RESPONSE TO SOY ISOFLAVONES IN WOMEN	IOWA STATE UNIVERSITY OF SCIENCE & TECH.	Soy protein rich in isoflavones (estrogen-like compounds) has been shown to prevent bone loss in ovariectomized rats. Our short-term preliminary study results in perimenopausal women are compelling, suggesting a bone-sparing effect. These findings have prompted great interest in isoflavones as an alternative to hormone replacement therapy, yet the long-term efficacy of isoflavones on bone in humans is unknown. Our objective is to determine the three-year efficacy of isoflavone-rich soy extract in attenuating bone loss in postmenopausal women. The central hypothesis is that soy isoflavones will attenuate bone loss in early postmenopausal women by maintaining bone formation, being modulated by growth factors and isoflavone metabolism. The rationale for this research is that current hormone therapy is fraught with side effects that adversely affect women, resulting in non-compliance. This randomized double-blind placebo controlled clinical trial will examine the effects of two doses (80 or 120 mg/d) of isoflavone-rich soy extract on bone in non-osteoporotic early postmenopausal women (N=234). Specific Aims are to: 1) Determine the bone-preserving effects of isoflavones on lumbar spine bone mass as the primary outcome; 2) Relate treatment-induced changes in bone mass to changes in biochemical markers of bone turnover; 3) Identify potential mechanisms by which isoflavones prevent or modulate bone loss by measuring endogenous estrogens, sex hormone-binding globulin, insulin-like growth factor-I (IGF-I), urinary minerals, serum 25(OH)vitamin D, plasma isoflavones and their metabolites, and customary intake of isoflavone-containing soy, thus accounting for variability in response to treatment; 4) Ascertain the safety of isoflavone-rich soy extract. Caucasian women of European descent will be recruited at two sites (117 at IA, 117 at CA). Random effects repeated measures analyses will be used to: a) characterize change in bone mass as the primary outcome, b) estimate treatment-induced effects, and c) depict change in markers of bone turnover in relation to bone mass change. We will use intent-to-treat for the primary test. We will also examine potential modulators (reproductive hormones, IGF-I, plasma isoflavones) and account for other factors that affect bone, as indicated in specific aim 3. This study will provide valuable data on whether isoflavones impact bone in early postmenopausal women and help elucidate potential mechanisms, thereby contributing to our understanding of isoflavones as an alternative to traditional hormone therapy.
AR047342	HOROWITZ, MARK	REGULATION OF BONE REMODELING BY MEGAKARYOCYTES	YALE UNIVERSITY	Bone marrow is the source of osteogenic, hematopoietic, and immune cells. The close juxtaposition of these cells makes the bone marrow the focus for many of the regulatory interactions required for homeostatic development of bone. Recent data indicate that hematopoietic cells can influence the differentiation of osteogenic cells. It has been suggested that one such cell, the megakaryocyte, is unique by being the only cell, other than osteoblasts and odontoblasts, to express the matrix proteins osteocalcin and bone sialoprotein. The Principal Investigator has begun an analysis of chimeric mice deficient in either GATA-1 or NF-E2, transcription factors involved in the differentiation of megakaryocytes. These animals experience a developmental block in megakaryocyte differentiation resulting in a phenotype characteristic by greately-increased numbers of megakaryocytes in the spleen and bone marrow with concomitant drastic reduction or total absence of mature platelets. Preliminary data indicate these mice also develop strikingly increased trabecular and cortical bone mass, with increased bone formation, increased numbers of osteoblasts and normal numbers of osteoclasts. It is hypothesized that the megakaryocytes are the causative agent of the increased bone formation in these mice. Four specific aims will be pursued: 1) Quantitative analysis of the bone phenotype in GATA-1 knockdown and NF-E2 knockout mice; 2) Quantitative functional analysis of mutant and control osteoblasts in vitro; 3) Quantitative functional analysis of mutant and control megakaryocytes in vitro; and 4) Functional analysis of the megakaryocyte-osteoblast interaction. The long-term goal of this proposal is to identify the mechanism(s) by which the megakaryocytes induce the marked increase in bone formation. These studies will show how megakaryocytes regulate osteoblast differentiation or function and further identify the interactions between hematopoietic and osteogenic cells. It is well established that once the skeleton starts to lose bone, whether from age, **menopause**, or other causes, it is difficult, if not impossible, to build bone mass. No anabolic agent is available which adds significant amounts of new bone to the skeleton. Therefore, new models of bone formation present the potential to discover new unrecognized anabolic pathways. This is particularly true for in vivo models with an established bone phenotype. Such information would be applicable to a wide variety of skeletal defects including post-menopausal osteoporosis, age-related osteopenia, fracture repair, and extended survival of prosthetic implants.

rant Number	PI Name	Project Title	Institution	Abstract
AR047368	KIEL, DOUGLAS	OSTEOGENIC MECHANICAL STIMULI-PREVENT/REVERSE BONE LOSS	HEBREW REHABILITATION CENTER FOR AGED	Therapies which increase bone formation are highly desirable, yet few are available, and those under investigation, have significant disadvantages. Extremely low magnitude (less than 10 microstrain) biomechanical stimuli, intended to supplant the deterioration of muscle dynamics which parallel the aging process, can be introduced non-invasively into the skeleton as a non-pharmacologic means of increasing bone mass and strength. In animal studies, we have demonstrated that short periods (less than 30 min) of mechanical loading, applied at a relatively high frequency (15-90 Hz), will increase trabecular volume and number, mineral apposition rate and labeled surface, and will decrease trabecular spacing. Moreover, a one-year double-blind placebo controlled clinical trial of mechanical stimulation in 55 post- menopausal women, exposed to short duration (20 minute), low magnitude (0.2 g), 30 Hz mechanical stimuli demonstrated that lumbar spine bone mineral density (BMD), normalized for body weight, declined by 3.3 percent BMD in the control group compared to only 0.8 percent in the treated group. Similarly, in the trochanter region of the hip, a 2.8 percent loss was observed in the control group while the treated group experienced a 0.4 percent gain. Stratified for body mass index, it was clear that the efficacy of treatment was greatest in thinner women (BMI less than 24 K g/m2). The biomechanical stimulation was very well tolerated. The central hypothesis of this proposal is that osteogenic mechanical stimulation (0.3g at 30 Hz for 10 minutes daily) will effectively inhibit the rapid bone loss that immediately follows the **menopause**, and will serve to reverse bone loss in a population of frail elderly women. These two principal hypotheses will be addressed in a prospective, double blind, multi-center trial in which two experimental groups will be studied: women 1-6 years past the **menopause** (100 subjects), and women greater than 70 years of age (50 subjects). The recently menopausal women will have a hip T-score (TOTAL, neck, trochanter or intertrochanter) between -0.5 and -1.5 while the elderly participants will have T-scores less than -1.5. All women will be of thin body stature (body mass index below 26 kg/m2). In the feasibility trial, described above, it was women of this body and BMD status that were most responsive to the biomechanical treatment. The primary outcome variable, bone mineral density at the hip, will be measured at baseline and at 12-month intervals for three years. Secondary outcome variables will include BMD at the spine, and indices of bone formation and resorption, as well as the effect of these interventions upon postural stability, another key risk factor for fracture. We anticipate that the results of this study will demonstrate the attributes of a unique osteogenic biomechanical therapy for osteoporosis.
AR047659	CUMMINGS, STEVEN	UCSF-KAISER WOMEN'S HEALTH INTERDISCIPLINARY SCHOLARSHIP	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	The University of California, San Francisco (UCSF) and the Division of Research (DOR) for Northern California Kaiser (Kaiser) join in **Women**'s Health Interdisciplinary Scholarship Program for Research (WHISPR) program to train successful and independent clinical investigators in **women** health and chronic diseases. We have organized our strengths in **women**'s health and chronic disease into 12 Interdisciplinary Research Areas: 6 disease areas (Cardiovascular; Breast Cancer; Skeletal Health; Neuropsychiatric Disorders -- Dementia, Depression; Substance Abuse; Urinary Incontinence; and HIV in **Women**) and five cross-cutting research areas (Sex Hormones, Woman's Imaging. Complementary and Alternative Medicine, Health Services Research, and **Aging**). 12 senior faculty (7 **women**), serve as Senior Mentors. All Senior Mentors have successful research careers in **women**'s health or relevant chronic diseases and strong track records of training and mentoring. UCSF and Kaiser train over 350 fellows annually and have many other clinical faculty who would be excellent candidates for this Scholarship. We will also recruit talented and diverse Scholars from outside UCSF and Kaiser. In consultation with her Senior Mentor, each Scholar will develop a Training Plan tailored to her background and interests. The Plan starts with coursework, drawn from UCSF's Clinical Research Training Program and Program in Biomedical Science. Each Plan is built around milestones toward independence: publications, presentations and independent funding. Scholarships will last 2 or 3 years, depending on the Scholar's background. Scholars who want time for family caregiving may plan 1/2 or 2/3-time programs that last 3 or 4 years. A Core Seminar in **Women**'s Health will teach scholars about a range of **women**'s health issues from biological to social aspects of gender and disease. Scholars, Senior Mentors and our Advisory Board will meet in an annual retreat to strengthen relationships and reevaluate the program. Dr. Steve Cummings, Assist. Dean for Clinical Research at UCSF, Dr. Joe Selby, Director of the Kaiser DOR, and Dr. Deborah Grady, Vice Chair of the Dept of Epidemiology and Biostatistics (Program Director at UCSF) have major institutional roles that guarantee strong support for this Scholarship. For example, UCSF has given space to establish a Center for **Women**'s Health Research and Kaiser has committed salary support for Scholars. Our goal is to create a model national resource for training successful investigators in **women**'s health.
AR048354	SELLMEYER, DEBORAH	KCITRATE, THIAZIDES, OR COMBINATION TO PREVENT BONE LOSS	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	Osteoporosis and its sequelae pose a substantial health burden for postmenopausal **women**. One white woman in six will suffer a hip fracture during her lifetime, and mortality after hip fracture ranges from 12-20% in the first year. Nutritional supplements to optimize dietary intake can improve bone health. For example, dietary calcium and vitamin D intake is often sub-optimal; supplements can reduce bone loss and fracture risk. Less well known is that the typical diet of industrialized nations is also deficient in potassium and base precursors (fruit and vegetables) while being rich in acid precursors (protein). The lack of dietary base precursors results in a mild metabolic acidosis that becomes progressively worse due to age related declines in renal function. Even the mild degrees of metabolic acidosis that occur with **aging** increase urinary calcium excretion, bone resorption, and urinary nitrogen excretion as base is mobilized from bone and muscle to buffer the dietary acid. These changes can be reversed by dietary supplementation with base as an alkaline potassium salt (e.g. potassium citrate). Combination therapy with a thiazide diuretic and an alkaline salt of potassium lowers urinary calcium excretion even further. To test the hypothesis that supplementation with oral potassium citrate, thiazide diuretic, or combination therapy with both agents will reduce bone and muscle mass loss over three years in postmenopausal **women**, they plan a randomized, double-blind, placebo-controlled trial. This will be a large multi-center study with an estimated sample size of 3220 participants, requiring extensive development and planning. Therefore, they are submitting this proposal for a planning grant to develop the specific elements essential for a successful full-scale clinical trial including strategies for recruitment of participants, experimental design and protocols, data management, analytical techniques, administrative procedures, and collaborative arrangements.

rant Number	PI Name	Project Title	Institution	Abstract
AR048841	LANE, NANCY	MIDCAREER INVESTIGATOR AWARD PATIENT-ORIENTED RESEARCH	UNIVERSITY OF CALIFORNIA SAN FRANCISCO	Nancy E. Lane, MD is an Associate Professor of Medicine at the University of California, San Francisco (UCSF). She is an established clinical investigator in musculoskeletal diseases with a special emphasis on osteoporosis and osteoarthritis. She is currently an NIH-funded investigator conducting a study to determine if PTH can reverse glucocorticoid-induced osteoporosis and to determine risk factors for the development and progression of hip OA. The purpose of this K24 award is to mentor and teach clinical research in osteoporosis and osteoarthritis at UCSF by 1) Developing an interdisciplinary clinical research seminars in osteoporosis and osteoarthritis that both topical lectures and work in progress research presentations by junior investigators; 2) Meeting individually with all junior clinical investigators UCSF in the field of osteoporosis and osteoarthritis to review research progress, provide study design analysis suggestions, and to establish additional resources for the investigators; 3) Becoming a core faculty member in the Master's in Clinical Research Program at UCSF by teaching a seminar on Developing a Clinical Research Protocol and mentoring master's students on research methodology; 4) Mentoring junior investigators in clinical research with my currently funded NIH grants on glucocorticoid-osteoporosis and on the epidemiology of hip OA. The specific aims of the currently funded NIH proposal to determine if PTH can reverse glucocorticoid-induced osteoporosis are to: I) To determine the changes in BMD caused by two years of treatment with hPTH (1-34) or placebo in postmenopausal **women** with GC-induced osteoporosis who are taking estrogen, calcium, vitamin D and chronic low doses of GCs; 2) To determine if estrogen or alendronate will preserve the high bone mass state created by two years of hPTH (1-34) treatment; 3) To determine the association of biochemical markers of bone turnover with hPTH (1-34) both during and after treatment. Monitoring for specific aim 3 will be accomplished by obtaining serum bone specific alkaline phosphates, serum osteocalcin, and urinary deoxypyridinoline cross-links at 3-month intervals; 4) To compare, as possible, the fracture incidence between the hPTH (1-34) and placebo treatment groups. Monitoring for specific aims I and 2 will be accomplished by annual spinal and proximal femur trabecular bone mineral content by quantitative computed tomography (QCT) and semi-annual dual x-ray absorptiometry (DXA) of the spine, hip, and forearm. The specific aims for the natural history of hip CA are to identify cases of new or worsening radiographic osteoarthritis (OA) of the hip by obtaining a second x-ray of the pelvis after an average of 8 years of follow-up in order to describe the natural history of radiographic hip OA and to determine the risk factors for hip OA. This Study of Osteoporotic Fractures cohort of elderly Caucasian **women** age - 65 have had radiographs of the pelvis obtained at baseline and after 8 years of follow-up in addition to bone mass measurements and other questionnaire and medication information. The data have been obtained and analyses are required. Dr. Lane has the enthusiastic support of her department of medicine and epidemiology at UCSF to pursue both her mentoring and continued research efforts in-patient oriented clinical research goals. She will strengthen her role senior mentor to young clinical investigators, she will teach clinical research methodology and develop a strong interdisciplinary clinical research group for musculoskeletal disease oriented research at UCSF.
AR049501	NELSON, DOROTHY	PREVENTING BONE LOSS IN BLACK MEN WITH PROSTRATE CANCER	WAYNE STATE UNIVERSITY	It is well established that abrupt cessation of sex **hormone** production in men and **women** causes bone loss. Several studies have demonstrated that androgen deprivation **therapy** (ADT) in men with prostate cancer increases the risk of osteoporosis and fractures. As the age at diagnosis of prostate cancer decreases, the use of ADT increases, and life expectancy improves, more men will be living a substantial portion of their lives with sex **hormone** deficiency and a higher risk of osteoporotic fracture. We propose a planning grant for a future clinical trial that will compare the efficacy of intervention with bisphosphonate **therapy** (with calcium and vitamin D), versus calcium and vitamin D alone, in men with prostate cancer who are being treated with ADT. Specifically, we plan to study African-American men, who have been underrepresented in other such trials. We plan a 2-year, randomized, double-blind trial of once-weekly oral bisphosphonate **therapy** plus daily calcium and vitamin D supplementation, compared with once-weekly placebo and daily calcium and vitamin D supplementation. Either alendronate or risedronate will be used for the bisphosphonate arm, to be determined during the planning phase. Bone density, biochemical markers of bone turnover, and body composition will be measured at regular intervals. Measures of free testosterone and gonadotropins will be obtained as part of routine clinical care. Fractures will be noted. The specific aims for the proposed planning grant include identification of additional clinical sites and clinical coinvestigators; refinement of the study design, including choice of bisphosphonate, sample size, and randomization scheme; development of a strategy to maximize recruitment and retention; preparation of a manual of procedures; and organization of a data safety monitoring committee. We believe that this planning period will allow us to develop specific elements essential to the success of the proposed trial without adding a lengthy organizational period to the actual trial. We also want to ensure that culturally sensitive, effective recruitment tools are in place.
AR049701	MAJUMDAR, SHARMILA	VERTEBRAL FRACTURE: TRABECULAR BONE STRUCTURE ASSESSMENT	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	Osteoporosis is a condition characterized by a reduction in the bone mineral density, impaired bone quality and frequent occurrence of fractures resulting from minor trauma. Current assessment of osteoporotic fracture risk is based on bone densitometry techniques that do not entirely predict fracture risk or the impact of a particular intervention. Bone quality encompasses bone geometry and macro-architecture, trabecular bone structure, matrix calcification, bone turnover. The quantitative analysis of bone structure and the elucidation of relationships between structural parameters and bone strength may have a major impact upon the prediction of fracture risk and evaluation of different therapies. In this application, we are proposing to extend our previous work and make use of recent advances in hardware and software, to obtain three-dimensional (3-D) magnetic resonance (MR) images with resolutions of approximately 100x 100x300 microns so as to accurately quantify the 3-D architecture of the trabecular bone network in the radius, calcaneus and proximal femur, and perform a rigorous evaluation of the impact of these data on the pathophysiological changes in skeletal bone and trabecular micro-architecture in aging, osteoporosis and fracture susceptibility. The specific aims of this study will be to establish non-invasive, reproducible imaging surrogates that can be used to assess bone quality in vivo. MR image derived parameters of trabecular micro-architecture at the different measurement sites will be related to age, **menopause** status and osteoporotic status in a cohort of 250 subjects. The primary question that will be addressed is whether MR assessment of trabecular micro-architecture at the radius, calcaneus and proximal femur, combined with bone mineral density, provide a means to explain the discrepancy between bone mineral density and fracture occurrence. We will assess whether using MR derived measures of trabecular bone at the different skeletal sites show site specific differences, relationship between structure and bone mineral density at these sites, and whether these measures may be used to complement bone mineral density measurements in the study of osteoporosis.

rant Number	PI Name	Project Title	Institution	Abstract
AR092237	RECKER, ROBERT M.	HORMONE REPLACEMENT THERAPY WITH ALENDRONATE IN POST MEN	CREIGHTON UNIVERSITY	The purpose of this contract is to conduct a randomized, double-blind, controlled trial of a combination of low-dose, continuous hormone replacement (o.d mg/day conjugated equine estrogens, +2.5 mg/day medroxyrpogesterone) with alendronate (10mg/day). The two drugs will each be tested alone and in combination in estrogen deprived, osteopenic, postmenopausal women over 60 years of age. Each of the three groups will enroll 72 participants and follow them for three years. Calcium and Vitamin D supplements will be given to all participants throughout the study. The hypothesis that will be tested is that the combined therapy shows a greater bone effect than either drug given alone. The primary outcome measures will be spine bone mineral density, total hip bone mineral density, and total body bone mineral content.

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 portfolio includes a broad array of basic and clinical research on women's reproductive health, including studies that may relate directly or indirectly to (1) menopause; (2) other conditions that may be associated with physiological changes that occur in menopause; (3) hormone replacement therapy (HRT); and (4), alternatives to HRT. This overview summarizes only those NICHD projects that target these topics.

NICHD research on health risks associated with HRT may better enable women and clinicians to evaluate such risks and may result in better treatments for conditions associated with menopause, notably osteoporosis. For example, in a study of menopausal hormone replacement, data from NICHD intramural investigators suggest that the addition of an androgen (male sex hormone) to HRT may reduce the severity of, or prevent, estrogen-induced increase in breast cancer. In other research, an investigator is developing an implantable, biodegradable means of delivering estrogen replacement therapy to women for a longer period of time than is possible with currently-available methods of delivery.

Other researchers supported by the NICHD are using data and specimens previously collected from women participating in the Heart and Estrogen Replacement Study (HERS). They are investigating an observation that women with a certain genotype (genetic makeup), who are using estrogen-only HRT, experience much greater increases in HDL (high density lipoprotein) cholesterol than those with other genotypes. Results of the current investigation could lead to fundamentally important new knowledge about the action of estrogen in women's bodies and the regulation of HDL cholesterol. Ultimately, results could also enable women and clinicians to better assess benefits and risks of HRT. In another study, the principal investigator is using a mouse model to study how estrogen influences bone growth and metabolism. This investigator's long-term goals are to improve understanding of the disease process in osteoporosis and to lay the groundwork for new ways to diagnose and treat this disease.

Another NICHD study relating to osteoporosis is a clinical trial, in women with premature ovarian failure (i.e., failure of ovary function before age 40), of estrogen hormone replacement with and without the addition of an androgen. As with later-occurring menopause, women with premature ovarian failure are at risk of losing bone density. They also have abnormally low levels of androgens in their blood, which may contribute to osteoporosis risk. Because the same HRT commonly used in older, menopausal and postmenopausal women may not adequately protect the younger women from osteoporosis, investigators hypothesize that using an estrogen/androgen combination could provide better protection.

Researchers are also trying to develop a mathematical model that can better predict the endocrine-related events associated with menopause. These models will link women's

menstrual, reproductive, and health-related histories to their experiences of menopause, taking into account such factors as the effects of hormones on menstrual bleeding during the perimenopausal period, and the natural decline in the number of eggs in the ovaries. This research will provide an important foundation for future epidemiological studies of women's health in relation to the natural ending of their reproductive function.

Other NICHD research targets conditions that may be associated with physiological changes associated with menopause, such as pelvic organ prolapse (POP), a condition for which older women are at greater risk. In one study, investigators are trying to identify factors that influence the onset and progression of POP. In another study, researchers are using an experimental animal (primate) to test hypotheses that (1) hormonal deprivation may contribute to prolapse; and (2) appropriate HRT could reverse weakening of the vaginal wall, a condition associated with POP. Another study focuses on Stress Urinary Incontinence (SUI), a common symptom of pelvic floor dysfunction that is associated with vaginal delivery and advancing age in women. Researchers are investigating whether declining levels of certain hormones may precipitate post-menopausal SUI. Using an animal model, they are studying the possibility of using steroid hormones to better treat this condition.

National Institute of Child Health and Human Development
Menopause Related Research

ID	TITLE	Name	INST	FY
F32HD07994	OVARIAN FUNCTION IN RURAL BANGLADESHI FEMALES	HOLMAN, DARRYL J	PENNSYLVANIA STATE UNIVERSITY-UNIV PARK	98
K08HD01463	THE ROLE OF ESTROGEN IN BONE METABOLISM	OZ, ORHAN K	UNIVERSITY OF TEXAS SW MED CTR/DALLAS	00-02
P30HD28138 037	AGING AND THE HYPOTHALAMIC-PITUITARY REPRODUCTIVE AXIS	HALL, JANET E	MASSACHUSETTS GENERAL HOSPITAL	98
P30HD28138 043	DEPRESSION AND HYPOGONADISM	HARLOW, BERNARD L	MASSACHUSETTS GENERAL HOSPITAL	98
P30HD28263 026	BIODEMOGRAPHIC MODELS OF REPRODUCTIVE AGING	WOOD, JAMES W	PENNSYLVANIA STATE UNIVERSITY-UNIV PARK	98-00
R01HD34159	BIODEMOGRAPHIC MODELS OF REPRODUCTIVE AGING	WEINSTEIN, MAXINE A	GEORGETOWN UNIVERSITY	98-01
R01HD34482	HORMONE REPLACEMENT AND RISK OF UTERINE FIBROID GROWTH	KJERULFF, KRISTEN H	UNIVERSITY OF MARYLAND BALT PROF SCHOOL	98-01
R01HD38673	MODEL FOR PELVIC FLOOR DISORDERS	CLARK, AMANDA L	OREGON HEALTH & SCIENCE UNIVERSITY	00-02
R01HD38679	MECHANISMS OF INCONTINENCE FOLLOWING VAGINAL DISTENSION	DAMASER, MARGOT S	LOYOLA UNIVERSITY MEDICAL CENTER	00-02
R01HD41131	NATURAL HISTORY OF POP-- A PROSPECTIVE COHORT STUDY	NYGAARD, INGRID E	UNIVERSITY OF IOWA	01-02
R01HD43355	ESTROGEN RECEPTOR VARIANCE AND CHD RISK IN HERS	HERRINGTON, DAVID M	WAKE FOREST UNIVERSITY HEALTH SCIENCES	02
R03HD36518	OVARIAN TOXICITY OF GALACTOSE	HUGHES, CLAUDE L, JR	CEDARS-SINAI MEDICAL CENTER	99
R29HD37360	AGING OF THE NORMAL HUMAN OVARY FROM BIRTH TO MENOPAUSE	KLEIN, NANCY A	UNIVERSITY OF WASHINGTON	98-02
R41HD36579	BIODEGRADABLE IMPLANT FOR ESTROGEN REPLACEMENT THERAPY	MONKHOUSE, DONALD	THERICS, INC.	98

U01AG12505	POPULATION STUDY OF MENOPAUSE IN AFRICAN AMERICAN WOMEN	POWELL, LYNDA H	RUSH-PRESBYTERIAN-ST LUKES MEDICAL CTR	98
U01NR04061	PERIMENOPAUSE, BONE AND ARTHRITIS IN AFRICAN AMERICANS	SOWERS, MARY F	UNIVERSITY OF MICHIGAN AT ANN ARBOR	98
Z01HD00628	REGULATION OF GROWTH AND REPRODUCTION	BONDY, CAROLYN A	NICHD	98-02
Z01HD00633	OVARIAN FOLLICULOGENESIS	NELSON, LAWRENCE M	NICHD	98-02

NATIONAL INSTITUTE ON DEAFNESS ANDCOMMUNICATION DISORDERS

(NIDCD)

National Institute on Deafness & Other Communication Disorders

Menopause Related Grants

Grant Number	Title	Principal Investigator	Institution
R01DC02236-09	GENES INVOLVED IN THE DEVELOPMENT OF VESTIBULAR OTOCONIA	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

Skeletal Bone Mineral Density Measure and Osteoporosis: This study of osteoporosis and oral bone loss is being conducted on a sub-sample of participants enrolled in the observational component of the NIH-supported Women's Health Initiative (WHI). Data from the core WHI includes sociodemographic information, a comprehensive medical history and hipbone mineral density (BMD) test using dual energy x-ray absorptiometry. In addition, these women will receive a comprehensive assessment of oral hard tissues at baseline, three-years and six-years. Components of the oral assessment include a dental history, full mouth oral examination and standardized radiographs to determine bone height and density. The study will look at relationships between the BMD and oral bone density assessments derived from a validated technique known as digital subtraction radiography. To date, a total of 200 women have been enrolled in the study.

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.

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 first year and it is actively enrolling women. Their target is to enroll 1000 subjects from a total of 1348 eligible postmenopausal women.

National Institute of Dental and Craniofacial Research

Menopause Related Projects – FY 2002

Contract or Grant Number	Title	Principal Investigator	Institutions
NO1 DE052605	Skeletal Bone Mineral Density Measures and Osteoporosis	Jeffcoat, Marjorie	University of Alabama at Birmingham
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

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 (DPP)/Mechanisms of Action in DPP Interventions: 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 will examine 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. The ORWH has provided support for a number of ancillary studies to the original DPP study. One study is assessing the correlation between glucose intolerance, insulin resistance and androgenic profile, as well as the effect of the various DPP treatment modalities and their mechanism of action, in pre- and perimenopausal women of different ethnic backgrounds in the DPP cohort. (KITABCHI, ABBAS R01 DK053061)

Genetic and Biochemical Predictors of Type 2 Diabetes Mellitus in Women: Diabetes mellitus is a major and increasing public health problem, affecting an estimated 17 million Americans, of whom 16 million have type 2 diabetes[d]. 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)

[d] 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, 2000. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, 2002.

Obesity

Weight Control in Peri- and Early Postmenopausal Women: Obesity is a preventable condition that contributes significantly to morbidity and mortality. This study is assessing the effectiveness of a modest lifestyle intervention program on preventing gains in body weight, whole body adipose tissue mass, and abdominal adipose tissue during a two-year period in perimenopausal and early postmenopausal women who are at risk for obesity. The results of this project may provide valuable information regarding lifestyle programs that may assist women in controlling body weight at a time when weight gain is common. (RACETTE, SUSAN B. R01 DK057461)

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 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. Since 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[e]. (LOVEJOY, JENNIFER R01 DK050736)

Profile-Based, Internet-Linked, Obesity Prevention Trial: The increasing prevalence of obesity and its co-morbidities and the limited success of previous weight loss/maintenance interventions argue for the need for new approaches to prevent obesity. Perimenopausal women are at high-risk to develop overweight and obesity. This trial is developing and testing an innovative individualized weight loss/maintenance program for overweight perimenopausal women, driven by frequent assessment of the subject's biopsychosocial profiles--allowing timely intervention response to individual needs. The intervention is delivered through extensive use of new communication technologies--primarily an Internet-CD-ROM package--which have been largely unexplored in behavioral and biological research. The Internet technology represents a potentially low cost and effective means for providing the continuous education, encouragement and social support to foster sustained behavior change and weight loss/maintenance. (GOING, SCOTT B. R01 DK057453)

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

[e] 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.

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 approximately 5,000 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. Equal numbers of men and women will be enrolled and at least 33 percent of the participants will come from ethnic minority groups. Look AHEAD is collecting self-report data on women's health, including questions about history of pregnancies, use of hormone medication, and menopausal status. This study has already enrolled 80 percent of the study participants, and expects to meet its recruitment goals. Other sponsoring institutes and 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[f]. (DORMAN, JANICE S. R01 DK044590)

Bone Loss and Osteoporosis

Role of IL-6 and Estrogen in PTH-Induced Bone Resorption: Osteoporosis affects approximately 10 million persons in the U.S., 80 percent of whom are women[g]. Both preventive and improved treatment strategies are needed to staunch current disease and reduce women's vulnerability to this disorder, which rises dramatically post-menopause. Considerable attention has focused recently on understanding the cellular mechanisms by which bone loss (resorption) occurs in osteoporosis. Evidence indicates that parathyroid hormone (PTH) has an important role in mediating this phenomenon. The goal of this study is to further delineate the role of the cytokine interleukin-6 (IL-6) in mediating the resorptive effects of PTH *in vivo*, and to continue to investigate the hypothesis that the increased skeletal sensitivity to PTH in the estrogen-deficient state is mediated by augmented PTH-induced IL-6 production. The study will include an investigation of the newly formed hypothesis that observed racial differences in the resorptive response to PTH infusion in postmenopausal women are due to differential PTH-induced increases in the production of pro-resorptive cytokines. (MASIUKIEWICZ, URSZALA R03 DK061674)

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(1-36)) has many properties similar to PTH, can be safely administered to humans, and appears from preliminary clinical results to be a pure anabolic agent for the treatment of postmenopausal osteoporosis when administered to women on estrogen therapy. 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,

---

[f] 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.

[g] National Osteoporosis Foundation http://www.nof.org/osteoporosis/stats.htm. Accessed August 19, 2003.

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 younger 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. This group has reported that diabetes under pharmacologic treatment is associated with increased risk of clinically apparent UTI in postmenopausal women[h]. A new study using this cohort (*H_2O_2-Producing Lactobacilli And Postmenopausal UTI*) is 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. (FIHN, STEPHAN D. R01 DK041341; GUPTA, KALPANA K23 DK2660)

Risk Factors for Urinary Incontinence in Women: This study will capitalize 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 plan to examine 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 will utilize 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. (GRODSTEIN, FRANCINE R01 DK062438)

Behavior and Stimulation Therapy for Stress Incontinence: Urinary incontinence in the elderly is a major problem with significant medical, psychological and social consequences. Previous research on stress incontinence has demonstrated that behavioral interventions and electrical stimulation are effective for many individuals. However, it is clear that no one method has been 100 percent effective and may have disadvantages. The broad objective of this study was to improve the treatment of stress incontinence by improving the efficacy of individual treatment modalities, by combining treatments that may have additive effects and by studying further the

[h] Boyko EJ, Fihn SD, Scholes D, Chen CL, Normand EH, Yarbro P. Diabetes and the risk of acute urinary tract infection among postmenopausal women. *Diabetes Care* 25:1778-83, 2002.

mechanisms by which therapies reduce incontinence. This research group recently reported results from this study demonstrating that pelvic floor electrical stimulation did not increase the effectiveness of a comprehensive behavioral program for women with stress incontinence[i]. (GOODE, PATRICIA S. R01 DK049472)

Urinary Incontinence Treatment Network (UITN): About 13 million Americans[j], most of them women, suffer from urinary incontinence, 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. http://www.niddk.nih.gov/fund/divisions/kuh/UITI.htm

[i] Goode PS, Burgio KL, Locher JL, Roth DL, Umlauf MG, Richter HE, Varner RE, and Lloyd LK. Effect of behavioral training with or without pelvic floor electrical stimulation on stress incontinence in women: a randomized controlled trial. *JAMA* 290:345-52, 2003.

[j] Urinary Incontinence in Adults: Acute and Chronic Management. Clinical Practice Guideline No. 2, 1996 Update. Rockville, MD: Agency for Health Care Policy and Research (AHCPR), DHHS; March 1996. AHCPR publication 96-0682.

NATIONAL INSTITUTE ON DRUG ABUSE

(NIDA)

National Institute on Drug Abuse

Menopause Related Grants

Grant Number	TITLE	PRINCIPLE INVESTIGATOR	INSTITUTION
1RO1DA01356	NATURAL HISTORY OF MENOPAUSE IN HIV INFECTED DRUG USERS	SCHOENBAUM, ELLIE	MONTEFIORE MEDICAL CENTER (BRONX, NY)
1K12DA014040	INTERDISCIPLINARY RESEARCH CAREERS IN WOMEN'S HEALTH	WILSON, EMERY	UNIVERSITY OF KENTUCKY
5R01DA011324	OFFICE BASED METHADONE PRESCRIBING II	DRUCKER, ERNEST	MONTEFIORE MEDICAL CENTER (BRONX, NY)

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

(NIEHS)

National Institute of Environmental Health Sciences

Menopause Related Grants

Grant Number	Title	Principle Investigator	Institution
5R01ES007171	FEMALE REPRODUCTIVE OUTCOMES AND TCDD EXPOSURE	ESKENAZI, BRENDA	UNIV OF CALIFORNIA BERKELEY
2P42ES007384	NEUROPHYSIOLOGIC DYSFUNCTION, LEAD MOBILIZATION, AND MENOPAUSE	BERKOWITZ, GERTRUD	MOUNT SINAI SCHOOL OF MEDICINE OF CUNY
5R01ES008979	ENVIRONMENTAL EPOXIDES—MECHANISMS OF OVOTOXICITY	HOYER, PATRICIA	UNIV OF ARIZONA
5R01ES008704	LEAD EXPOSURE, GENETICS AND OSTEOPOROSIS EPIDEMIOLOGY	KORRICK, SUSAN	BRIGHAM AND WOMEN'S HOSPITAL
1Z01ES049025	CAUSES AND CONSEQUENCES OF EARLY MENOPAUSE	COOPER, GLINDA	
1Z01ES04926	MENSTRUAL & REPRODUCTIVE RISK FACTORS FOR CANCER & CHRONIC DISEASE	COOPER, GLINDA	
1Z01ES049023	HORMONAL AND ENVIRONMENTAL FACTORS FOR SLE	COOPER, GLINDA	
1Z01ES049003	ENVIRONMENTAL EFFECTS ON FERTILITY	BAIRD, DONNA	
1Z01ES100490	STATISTICAL CONSULTING SERVICE: EPIDEMIOLOGICAL RESEARCH	PEDDADA, SHYAMAL	

NATIONAL INSTITUTE OF MENTAL HEALTH

(NIMH)

NIMH Current Menopause-Related Research				
Grant Number	**PI Name**	**Project Title**	**Institution**	**Abstract**
5K08MH001682	Altemus, Margaret	Estrogen Effects on Anxiety Related Neural Systems	Weill Medical College of Cornell University	The research component of this award focuses on investigating the hypothesis that estrogen restrains fear-associated behaviors. Data indicated that reproductive hormone fluxes, like those experienced during menopause and hormone replacement therapy, have profound effects on the course of anxiety disorders and depression. The aims of this research are to study the effects of estrogen on behavioral tests of anxiety, to examine the effects of estrogen on neuroendocrine systems known to modulate fear and anxiety, and to define the anatomic sites of estrogen action on fear behaviors.
1R01MH062677	Bethea, Cynthia L	Ovarian Steriod Regulation of Serotonin in Primates	Oregon Health & Science University	This application examines the manner by which estrogen and progesterone enhance serotonin neurotransmission within the primate brain. These studies are highly relevant to understanding how ovarian hormones affect neurotransmitter systems involved in the regulation of mood, cognition, and stress responsiveness. The results of these studies will be useful for understanding the distinct effects of single or combined hormone replacement therapy of post-menopausal women on neurotransmission.
2R01MH059689	Bromberger, Joyce T	Menopausal Transition, Mental Health and Ethnicity	University of Pittsburgh at Pittsburgh	This grant aims to assess whether women will be more likely to develop new or recurrent depression during the perimenopausal transition than before or after and to compare rates of new or recurrent depression across the transition for African American and Caucasian women. Studies under this grant will also determine if a history of major depression is a risk factor for depression, increased levels of perceived stress, somatic and psychological symptoms, and decreased quality of life or functioning during the menopausal transition.

R03MH63267	Curtis, Andre	Gonadal Hormones and the Locus Coeruleus System	The Children's Hospital of Philadelphia	This application will test the hypothesis that estrogen and progesterone regulate corticotrophin-releasing factor and/or opioid neurotransmission in the Locus Coeruleus. Studies will examine electrophysiological recordings of this region following stress exposure in male rats and ovariectomized female rats with or without hormone replacement therapy. These studies will address possible mechanisms responsible for the enhanced stress responses seen in females and may be relevant to understanding differences in vulnerability to stress-related psychiatric disorders between genders and across the female lifespan.
R03MH63932	Eckel, Lisa	Mechanism of Estrogen's Inhibitory Effects on Feeding	Florida State University	Studies proposed in this R03 examine the cellular mechanisms responsible for the anorectic effects of estrogen. Specific experiments test whether this effect in rats is due to increased sensitivity to the satiety signal produced by the hypothalamic peptide cholecystokinin (CCK). Results of these studies will be significant for understanding mechanisms through which estrogen regulates food intake and its role in the pathogenesis, course, or treatment of disordered eating in women across the lifespan.
5R01MH059891	Foster, Thomas C	Estrogen and Cognition Over the Lifespan	University of Kentucky	The long-term goal of this research is to understand the mechanisms for hippocampal-dependent memory function during aging. Estrogen treatment can delay the progression of memory loss associated with aging and Alzheimer's disease. This study tests the hypothesis that estradiol effects on memory are due to altered calcium homeostasis. It is believed that the results of the experiments will add to our knowledge concerning the regulation of synaptic function across the lifespan and provide a basis for understanding the mechanisms for estrogen's effects on memory.
1R01MH063089-01A1	Freedman, Robert F	Sleep Disturbance in Menopause	Wayne State University	This application proposes to investigate the relationship between hot flashes and sleep disturbance in perimenopausal women. Citing the hypothesis that hot flash-induced increases in body temperature cause microarousals that disturb sleep quality, this project will examine women with and without hot flashes using detailed sleep studies. Ambient room temperature manipulation and estrogen supplementation will also be examined for their effects on sleep quality and frequency of hot flashes.

R03MH65460	Frick, Karen	Estrogen - Cholinergic Interactions in Memory Modulation	Yale University	Some evidence suggests that estrogen can enhance cognitive function and spare memory loss with aging. However, the mechanism by which this occurs remains unknown. This proposal investigates the hypothesis that estrogen enhances spatial memory through interactions with the basal forebrain cholinergic system. Because the cholinergic system has been implicated in the pathology of Alzheimer's disease, the results of these studies could lead to improved treatments for this and other memory disorders associated with normal and pathological aging processes.
1Z01MH002659	Gold, Philip W	The Neurobiology of Major Depression	IRP	Depression may be a major risk factor for osteoporosis and abnormally elevated stress hormone levels may contribute to bone loss. This study will determine whether women with major depression lose bone mass at a faster rate than women without depression. This study will also determine if the drug aldendronate (Fosamax) can maintain or increase bone mass in premenopausal women with major depression and osteoporosis. It is hoped that these studies will lead to the development of preventive treatments for the increased bone loss typically seen in menopausal, depressed women.
1R01MH061817	Herndon, James G	Selective Estrogen Modulators and Cognition	Emory University	This application examines the effects of selective estrogen receptor modulators (SERMs) on cognitive function in rhesus monkeys and compares cognitive effects with effects on brain activity using PET imaging. Studies will examine whether the SERMs tamoxifen and raloxifene mimic or antagonize the effects of estrogen in attention, object recognition memory, spatial memory, and working memory tasks in ovariectomized female monkeys. Results from these studies may help to clarify the effects of estrogen receptor ligands on cognition and to identify brain regions whose activity is selectively modified by SERMs during performance of a learning task. These studies may provide useful information on these potential alternatives to hormone replacement therapy.

5R01MH059847	Horvath, Tamas L	Gonadal Steroid Regulation of the Biological Clock	Yale University	The long-term goal of this research is to examine the relationship between hormone levels, circadian function, and behavior, and to determine if hormones regulate the activity of the biological clock. In particular, the focus is on estrogen regulation of cells in the suprachiasmatic nucleus and lateral geniculate nucleus. The results of these experiments will reveal the mechanisms via which hormonal signals can regulate components of the biological clock. The findings will provide new insights into the etiology of discomforting symptoms of menopause, including mood swings, sleep disorders, and hot flashes, all of which are tightly coupled to the activity of the biological clock.
5R01MH59890	Jennes, Lothar H	Neuroendocrine Mechanisms of Reproductive Aging	University of Kentucky	The overall goals of this research are to determine the changes that occur in the brain during reproductive aging and to reveal the underlying mechanisms that cause a gradual decline in the regularity of the estrous cycle, followed by a complete cessation of cyclicity adult female rats. The proposed studies will provide comprehensive information on the changes that occur in the regulatory input to the gonadotropin-releasing hormone neurons during reproductive aging and will determine if estradiol causes these changes.
K23MH66978	Joffe, Hadine	Physiology of Estrogen's Mood Effect in Menopausal Women	Massachusetts General Hospital	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.

R01MH60858	Leranth, Csaba	Estrogenic Effects on Hippocampal Theta Rhythm and Memory	Yale University	Based on the indications that estrogen administration appears to improve cognitive performance in subjects with Alzheimer's Disease and the confluence of issues surrounding estrogen benefits and risks, this proposal aims to provide much needed information concerning the potential mechanism by which estrogen exerts its effects on cognitive mechanisms by investigating the indirect modulation of estrogen's effects in the hippocampus, and therefore on memory, from pre-hippocampal regions which are known to contain estrogen receptors.
5 R01 MH59919	Parry, Barbara	Menopausal Depression: Chronobiological Basis	University of California San Diego	This research project examines the effects of hormone replacement therapy on mood and circadian rhythmicity in healthy, non-depressed post-menopausal women. Subjects will be treated for 8 weeks with estradiol, estradiol plus progesterone, or placebo. Sleep/wake patterns and activity levels will be monitored after one month of treatment. At the end of the treatment period, mood, biological rhythmicity and synchrony of sleep, activity patterns, temperature, and plasma hormone secretion (melatonin and gonadotropic hormones) will be evaluated. These studies will provide important insights into the effects of hormone replacement therapy on mood and behavior and could lead to new clinical treatment guidelines for menopausal women. In addition, this research provides a basis for future studies of hormone replacement therapy on mood and circadian rhythms in depressed menopausal women.
5R29MH057423	Rasgon, Natalie L	ERT, Depression, and Cognition in Postmenopausal Women	University of California Los Angeles	The pathogenesis of late-life depression and antidepressant therapeutic response may involve postmenopausal estrogen deficiency. Existing data suggest that estrogen replacement therapy (ERT) in post menopause enhances both mood and cognitive function. This research will evaluate serotonin and cognitive functions in postmenopausal depressed women compared with matched postmenopausal controls and will assess antidepressant treatment outcomes for postmenopausal depressed women. The impact of ERT on cognition will also be assessed in both depressed and control postmenopausal women. This research will provide a foundation for future investigations of the pathophysiology of reproductive-related mood disorders.

1Z01MH002765	Rubinow, David	Reproductive Endocrine Related Mood Disorders	IRP	This project studies reproductive endocrine-related mood disorders and develops endocrine models for these disorders in order to characterize the role of gonadal steroids in affective disturbance, including the effects of menopause, perimenopause, and hormone replacement therapy.
1Z01MH002537	Schmidt, Peter	Psychobiology and Treatment of Perimenopausal Mood Disorder	IRP	The goals of this project are to identify the mechanisms underlying the effects of gonadal steriods on the regulation of affective states, to identify the effects of aging, menopause, and gender on the neuroregulatory actions of gonadal steriods, to determine the therapeutic utility of hormonal therapies in mood disorders occurring during midlife and perimenopause, and to identify the predictors of antidepressant response to hormone therapy in reproductive endocrine-related mood disorders.
R01MH59970	Shors, Tracey-Rutgers	Stress and Memory Formation Across the Female Lifespan	Rutgers University	This project examines the neuronal and hormonal mechanisms that underlie sex differences in learning and responses to stressful experience. The experiments capitalize on the hormonal fluctuations that occur across the female lifespan during early development, puberty, post-partum, and menopause. They are designed to associate and dissociate changes in learning and stress responses to changes in hormones and the resulting changes in the hippocampus. These studies will provide insight into sex differences in mental illness, especially those experienced so frequently by women, including unipolar, post-partum, and post-menopausal depression, and Alzheimer's disease.
F31MH063551	Tropp, Jennifer	Effect of Estrogen on Hippocampal Single Unit Activity	University of Connecticut Storrs	It has been shown that estrogen has an effect on the anatomy and activity of the hippocampus. The main objective of this project is to investigate the dynamics of the firing patterns related to normal hormone cycling as well as estrogen depletion. The effects of the absence of estrogen and estrogen replacement in the hippocampus are a major focus of this grant. The findings from this study will have important implication for understanding the processes in which memories are formed and the potential therapeutic effect of estrogen in menopausal women.

5R01MH058448	Van De Kar, Louis D	Synergy Between SSRIs and Ovarian Hormones	Loyola University Medical Center	This grant tests the central hypothesis that estrogen acts synergistically with SSRI treatment of depression via complementary mechanisms to desensitize serotonin 1A (5-HT1A) receptor systems and produce antidepressant effects. This synergistic action could shorten the delay in the onset of the effects of SSRIs. The proposed studies will examine the mechanisms by which estrogen modulates 5-HT1A receptor signaling. These studies will provide the scientific basis for the development of improved therapeutic regimens and novel drugs that provide faster clinical improvement in women suffering from PMS, depression, bulimia, and anxiety disorders.

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

(NINDS)

National Institute of Neurological Disorders and Stroke
Highlights of Menopause-Related Research
Current July, 2003

Molecular Mechanisms of Estrogen Neuroprotection (Wang, K08 NS41342)
It has been noted that removing ovaries from female rats eliminates stroke protection seen in intact female rats, suggesting that female reproductive hormones are neuroprotective. This study will focus on the molecular mechanisms responsible, such as role of estrogen receptors, and how they protect the brain.

Hormone Replacement Therapy and Ischemic Stroke Severity (Bushnell, K23NS 41929-03)
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 study will seek to determine if there are differences in stroke severity and outcome between HRT users and women that are not using HRT, and to measure differences in any markers of the coagulation system in the acute stroke period.

Gender Differences in Stroke (Hurn, P01NS20020)
Estrogen has been considered to be protective in coronary heart disease, but it is not clear if it is a neuroprotectant for females or males. Preliminary findings in animals indicate that females have a better outcome after stroke than males, and that ischemic events can be altered by estrogen-priming of the cerebral vasculature and the brain. The purpose of this study is to determine if there are inherent sex-linked injury mechanisms for salvaging brain tissue after an ischemic event.

Pharmacologic Plasticity in the Presence of Pain (subproject-Sex Differences and Estrogen Dependency of Spinal Cord Analgesia) (Eisenach/Tobin, P01NS41386) Studies have noted differences between the sexes in analgesic responses to systematically administered drugs. Testing has shown that in rats and monkeys, there seems to be an estrogen-dependent increase in spinal cholinergic activity in females. This study will further examine in animals and humans, the magnitude and the pharmacology of increased sensitivity to cholinoceptive agents in females, and the mechanisms for this sensitivity.

Cerebral Ischemia in the Female (Hurn, R01NS33668)
Blood flow and energy metabolism in the brain is compromised during an ischemic stroke, which can lead to focused or widespread brain damage. The female hormone estrogen may aid in recovery from ischemia. The purpose of this study is to determine the extent of estrogen's effects on cerebral blood flow, energy metabolism and blood vessel reactivity during and after global ischemic stroke in both female and male subjects. Information derived from these studies should improve the current understanding of vascular function in women and address the role of estrogen as potential neuroprotective therapy for patients of either sex.

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 gender disparity are not fully understood. Sex 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. Cerebral ischemic events occur in both sexes at all ages; however, neurologic and neuropsycholgic evaluations 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.

Neurochemical Mechanisms of Visceral Pain (Traub, R01NS37424)
This investigator is studying irritable bowel syndrome (IBS) in an animal model. The long-term goal is to examine the effects of estrogen on spinal MNDA receptor-mediated processing of noxious and innocuous colorectal stimuli. Estrogen will be administered to ovariectomized rats to determine if it alters sensory processing, and if so, characterize any effects.

Sympathetic Nerve Remodeling in the Adult Uterus (Smith, R01NS39570)
Published studies show that sympathetic nerve density of the virgin rat uterus fluctuates throughout the estrous cycle. Nerve density decreases during estrogen administration and mice that lack a functional estrogen receptor have uteri that are hyperinnervated. The grantees will design studies to ascertain if raising plasma estrogen will suppress uterine neurotrophic factor production. Information gained may have direct applicability to the understanding of dysmenorrhea and autonomic dysfunction that occurs in menopause.

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 AD victims. Guinea pigs, transgenic mice and cell cultures will be used to test agonist and antagonist activity on estrogen receptors and regulation and metabolism of the A-beta protein.

Ovarian Steroid Hormones and Hippocampal Plasticity (Levy, R01NS41582) It has been observed that estradiol modulates long-term potentiation of certain neural synapses, which may result in enhanced memory. Estradiol also increases excitability of CA1 pyramidal neurons, and may cause changes in synaptic plasticity. Using appropriate testing methods in rats, the investigators will characterize the magnitude of the excitability of the hippocampal CA1 region, and ascertain if over time, synaptic plasticity is increased. This study will provide important insights for understanding the biological basis for memory problems that can occur with menopause.

Estrogen and Brain Control of Blood Pressure (Clark, U54NS41071) The incidence of cardiovascular disease in women increases dramatically following menopause, likely triggered by estrogen deprivation. Using a rat model, these studies will investigate whether estrogen deprivation results in increased blood pressure, and which estrogen-sensitive neurotransmitter systems and regions of the brain produce this cardiovascular effect. Important new information on the protective effects of estrogen on the neural regulation of blood pressure may be gained from these studies.

Hormone Regulation of Pain Perception (Quinones-Jenab, U54NS41073)
Women generally have lower pain thresholds and are less sensitive to morphine-like analgesics than men. The proposed studies will examine the influence of steroid hormones on pain and opioid sensitivity in a female rat model. The results may provide insight into pain management approaches for women utilizing estrogen replacement therapy after menopause.

Evaluation of Novel Epilepsy Treatment Approaches (Rogawski-Z01NS02877) The investigator is examining causes of, and treatment for, catamenial epilepsy, an increase in seizure frequency that many women with epilepsy experience near the time of menstruation.

NINDS Menopause Research Grants Active July 2003*			
Grant Number	**Title**	**Principal Investigator**	**Institution**
F30 NS 43951-01	In Vitro Studies of Steroid Receptors in NF-1	Fishbein, L.	University of Florida
F31 NS 43897-01	Estrogen Effects on Place Cells and Navigation Strategy	Bennett, J.	University of Washington
K08 NS 41342-03	Molecular Mechanisms of Estrogen Neuroprotection	Wang, M.	Johns Hopkins University
K23 NS 41929-03	Hormone Replacement Therapy and Ischemic Stroke Severity	Bushnell, C.	Duke University
P01 NS 20020-20	Mechanisms of Regulation of Cerebral Blood Flow (subproject: Gender Differences in Stroke)	Traystman, R.	Oregon Health and Science University
P01 NS 41386-02	Pharmacologic Plasticity in the Presence of Pain (subproject: Sex Differences and Estrogen Dependency of Spinal Cord Analgesia)	Eisenach, J.	Wake Forest University
R01 NS 33668-09	Cerebral Ischemia in the Female	Hurn, P.	Oregon Health and Science University
R01 NS 33978-08	Epidemiology and Genetics of Parkinson's Disease	Rocca, W.	Mayo Clinic
R01 NS 37424-04A1	Neurochemical Mechanisms of Visceral Pain	Traub, R.	University of Maryland
R01 NS 39570-04	Sympathetic Nerve Remodeling in the Adult Uterus	Smith, P.	University of Kansas
R01 NS 41017-04	Estrogen Modulation of Brain A-Beta Metabolism in Vivo	Gandy, S.	Thomas Jefferson University
R01 NS 41582-03	Ovarian Steroid Hormones and Hippocampal Plasticity	Levy, W.	University of Virginia
R01 NS 46072-02	Gender Differences in Cardiac Arrest/CPR	Traystman, R.	Oregon Health and Science University
R21 NS 43604-02	Epidemiology of Cognitive Dysfunction and Parkinson's	Ascherio, A.	Harvard School of Public Health
U10 NS 44450-02	Neuroprotection in Parkinson's Disease: Clinical Center	Burns, R.	Southern Illinois University
U54 NS 41071-03	Estrogen and Brain Control of Blood Pressure	Clark, J.	Meharry Medical College
U54 NS 41073-03	Hormone Regulation of Pain Perception	Quinones, V.	Hunter College
1Z01 NS 02877-10	Evaluation of Novel Epilepsy Treatment Approaches	Rogawski, M	NINDS Intramural Program

* This list does not necessarily represent projects funded in any one fiscal year.

NATIONAL INSTITUTE OF NURSING RESEARCH

(NINR)

NATIONAL INSTITUTE OF NURSING RESEARCH
Menopause Related Grants
FY 2003

Biobehavioral Health in Diverse Midlife Women (Lee- NR004259) An NINR investigator is describing the bio-psycho-social-cultural health environment of multi-ethnic groups of midlife women and the patterns of change over time in biological, psychosocial, and ethnic/cultural factors. Findings from this study will assist in understanding the relative contributions of women's physiologic, cultural, and psychological environments to their experiences of menopause, an area of research where little is known.

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.

Decision Making Regarding Hormone Replacement Therapy (Padonu – NR000132) The investigator is developing and testing an educational decision support intervention tailored for use with a community-based population of low income African-American menopausal women. The intervention is designed to support effective decision-making around menopausal health issues and Hormone Replacement Therapy (HRT) among African-American women, an emerging area of inquiry.

Exercise and Perimenopausal Symptoms: A Randomized Trial (Li- NR004946). For decades exercise has been recommended as a nonpharmacological means of ameliorating perimenopausal associated symptoms (PAS). The purposes of this study are to understand the role of exercise in promoting health in perimenopausal women and the effect of exercise and its synergistic effect on HRT on PAS in perimenopausal women. Study results may provide needed information about the nonpharmacogical management of PAS.

Women in Transition: The Crucial Years Before Menopause (Wurzburg- NR004799)
This multimedia resource targets midlife women in addressing key issues related to perimenopausal health and provides solutions and support to help minimize the health risks associated during the midlife period. Hosted by Debbie Allen, this two part video recently
received the Telly Award and the Freddie International Health Media Award.

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.

Hormone Replacement Therapy among Women with Disabilities (Becker-NR005051)

This study compares factors 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 was the strongest predictor 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.

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.

Breast Cancer Survivors: Exercise and Raloxifene (Schwartz- NR05084). Breast cancer survivors are at an increased risk for muscle, bone, and cardiovascular complications due to inactivity, menopause, chemotherapy and catabolic steroids. The purpose of this research is to test the effects of exercise and raloxifene in postmenopausal breast cancer survivors on measures of bone health and quality of life. Findings may provide important new information on the health needs of breast cancer survivors.

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.

Estrogen, Angina, Activity, and Quality of Life in Women (Missik- NR005245) Given the vasoactive effects of estrogen, researchers are testing a model examining the relationship between the use of estrogen replacement therapy (ERT) and the frequency and severity of angina, daily physical activity, and quality of life of postmenopausal women with cardiac disease. Interventions that support the adoption and long-term use of physical activity are sorely needed for postmenopausal women with cardiac disease.

Menopause Transition: Biobehavioral Models of Symptoms (Mitchell- NR04141) This longitudinal study seeks to characterize biobehavioral outcomes in women throughout menopausal transition stages. Findings to date do not support a relationship between ovarian hormone changes or menopausal transition and depressed mood, stress, or sexual functioning. Results do support a relationship between role burdens, demands of working, health status, history of sexual abuse and symptoms, perceived stress, and sexual functioning.

Venlafaxine for Hot Flashes Following Breast Cancer (Carpenter- NR005261) Hot flashes are the most severe and prevalent menopausal symptom reported by women with breast caner. Researchers are examining the effectiveness and toxicity of sustained release venlafaxine hydrochloride on hot flashes in women following treatment for breast cancer.
Results may provide for new approaches to hot flash management in women following breast cancer treatment.

Effect of Hormone Therapy and Raloxifene on Serum Lipids (Roddy- NR007564) This double-blind clinical trial seeks to compare the short-term effect of Raloxifene or HRT on serum lipids and lipoproteins of dyslipidemic postmenopsual women over time. Study findings may provide

insights regarding raloxifene as a potential primary prevention alternative for dyslipidemic postmenopausal women.

An Internet Study of Migraines in Perimenopausal Women (Moloney- NR005303) This study is testing the feasibility and acceptability of an internet based research method to describe the self-care practices and perceptions of perimenopausal women with migraine headaches. Study findings may help to clarify gaps in health care resources for migraine prevention/treatment and identify the usefulness of the internet in conducting phenomenological research.

Summary of Findings Relevant to Menopause

Finkelstein JS, Lee M LT, Sowers MF, Ettinger B, Neer RM, Kelsey JL, Cauley JA, Huang MH, Greendale GA. (2002) **Ethnic variation in bone density in premenopausal and early perimenopausal women: effects of anthropometric and lifestyle factors.** Journal of Clinical Endocrinology & Metabolism, 87(7): 3057-3067

Primary Question: Is the traditional view that bone density is highest in African-American women, next highest in Caucasians, and lowest in Asian women correct if other factors are taken into account?

Summary of Findings: The traditional view is only true when bone density is considered without adjustment for ethnic variation in factors that have major effects of bone density, particularly body weight. When bone density is adjusted for these factors, it remains highest in African-American women and is lowest in Caucasians. Depending on the skeletal site, adjusted bone density in Asian women is either similar to that of African-American or intermediate between African-Americans and Caucasians. These data help explain some of the well-known ethnic variations in fracture rates that heretofore have seemed paradoxical.

Mitchell, E.S., & Fugate Woods, N. (2001). **Midlife women's attributions about perceived memory changes: Observations from the Seattle Midlife Women's Health Study.** Journal of Women's Health Gender-Based Medicine, 10(4): 351-362.

Primary Question: How do women describe their attributions about memory changes?

Summary of Findings: In a sample of 230 women age 35-55, women identified six attributes related to their memory changes, which included getting older, role burden and stress, physical health, menstrual cycle changes/hormones, inadequate concentration, and emotional factors. Overall, women did not link menstrual cycle of hormone use to most types of memory changes. The researchers emphasized the need to clarify whether women's perceptions of memory changes are linked to their performance on cognitive tests.

Randolph, J.F., Sowers, M.F., Gold, E.B., Luborsky, J., Santoro, N., McConnell, D.S., Finkelstein, J.S., Korenman, S.G., Matthews, K.A., Sternfeld, B., & Lasley, B. (2003) **Reproductive Hormones in early menopausal transition: Relationship to ethnicity, body size, and menopausal status.** Journal of Clinical Endocrinology and Metabolism, 88(4): 1516-1522.

Primary Question: How do reproductive hormones in the early menopausal transition differ by ethnicity, menopausal phase, age, and body composition?

Summary of findings: Serum estradiol and sex hormones-binding globulin levels were lower in Japanese and Chinese women than in Caucasians, African-Americans, or Hispanics. Serum testosterone levels were lower in Hispanics than in women belonging to the other 4 ethnic groups. Serum DHEAS (dehydroepiandrosterone sulfate) levels were higher in Chinese, Japanese and Caucasian women than in African-American or Hispanic women. Serum DHEAS levels were negatively correlated with age but not menopausal status. There were no ethnic differences in serum follicle stimulating hormone levels, but it was highly correlated with menopausal status. All hormone concentrations were significantly correlated with body composition.

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

Primary question: How does the experience of the menopause differ in African-American and Caucasian women?

Summary of Findings: Caucasian women were primarily concerned about menopause as it altered physical appearance to be less congruent with the societal ideal of youth. In comparison, African-American women viewed menopause as a normal, even welcome part of life. A language of emancipation and awareness of gender-bias were prominent in women's stories regardless of menopausal status or race.

Sowers MF, Pope S, Welch G, Sternfeld B, Albrecht G. **The association of menopause and physical functioning in women at mid-life.** Journal of the American Geriatrics Society 2001;49:1485-1492.

Primary Question: Is limitation of physical functioning in women aged 40-55 years associated with the menopausal transition?

Summary of Findings: Even at the relatively early ages of 40-55 years, approximately 20% of women self-reported limitation in physical functioning. Surgical menopause, postmenopause and the use of hormones were more frequently observed among women with "some" and "substantial" physical limitation, even after adjusting for economic status, age, body mass, index, and race/ethnicity.

National Institute of Nursing Research

Menopause Related Grants

Grant Number	Title	Principle Investigator	Institution
NR007738	HOME vs. CENTER-BASED WEIGHT LOSS AND EXERCISE IN MENOPAUSE	DENNIS. KAREN	UNIVERSITY OF CENTRAL FLORIDA
NR004259	BIOBEHAVIORAL HEALTH IN DIVERSE MIDLIFE WOMEN	LEE, KATHRYN	UNIVERSITY OF CALIFORNIA SAN FRANCISCO
NR005084	BREAST CANCER SURVIVORS: EXERCISE AND RALOXIFENE	SCHWARTZ, ANNA	OREGON HEALTH AND SCIENCE UNVERSITY
NR004141	MENOPAUSE TRANSITION-BIOBEHAVIORAL MODELS OF SYMPTOMS	WOODS, NANCY	UNIVERSITY OF WASHINGTON
NR000132	DECISION MAKING REGARDING HORMONE REPLACEMENT THERAPY	PADONU, GEORGIA	MICHIGAN STATE UNIVERSITY
NR004799	WOMEN IN TRANSITION: THE CRUCIAL YEARS BEFORE MENOPAUSE	WURZBURG, GERARDINE	STATE OF THE ART, INC.
NR004946	EXERCISE AND PERIMENOPAUSAL SYMPTOMS: A RANDOMIZED TRIAL	LI, SULING	LOYOLA UNIVERSITY OF CHICAGO
NR004061	THE STUDY OF WOMEN'S HEALTH ACROSS THE NATION-MICHIGAN	SOWERS, MARYFRAN	UNIVERSITY OF MICHIGAN AT ANN ARBOR
NR005261	VENLAFAXINE FOR HOT FLASHES FOLLOWING BREAST CANCER	CARPENTER, JANET	VANDERBILT UNIVERSITY
NR007564	EFFECT OF HORMONE THERAPY AND RALOXIFENE ON SERUM LIPIDS	RODDY, SHIRLEY	UNIVERSITY OF NEBRASKA MEDICAL CENTER
NR005281	HEART DISEASE IN WOMEN: ESTROGEN EFFECTS ON HEMODYNAMICS	SHERWOOD, ANDREW	DUKE UNIVERSITY
NR005339	ESTROGEN/PLATELET INTERACTION IN CEREBRAL ISCHEMIA	KEARNEY, MARGUERITE	JOHNS HOPKINS UNIVERSITY
NR005051	HORMONE REPLACEMENT THERAPY AMONG WOMEN WITH DISABILITIES	BECKER, HEATHER	UNIVERSITY OF TEXAS AUSTIN
NR005245	ESTROGEN, ANGINA, ACTIVITY AND QUALITY OF LIFE IN WOMEN	MISSIK, EUGENIA	KENT STATE UNIVERSITY @ KENT
NR05303	AN INTERNET STUDY OF MIGRAINES IN PERIMENOPAUSAL WOMEN	MALONEY, MARGARET	EMORY UNIVERSITY

NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE

(NCCAM)

National Center for Complementary and Alternative Medicine

NIH Research and Other Efforts Related to the Menopausal Transition

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" healthcare practices. NCCAM groups CAM practices within five major domains: (1) alternative medical systems (i.e., traditional Chinese medicine, Naturopathic Medicine, Ayurveda); (2) mind-body interventions, (i.e., meditation, biofeedback); (3) biologically-based treatments (i.e., herbal therapies, special diets); (4) manipulative and body-based methods (i.e., Chiropractic, massage); and (5) energy therapies (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 since, according to SWAN survey data, almost 50% of menopausal and perimenopausal women had used CAM therapies in the past year. Each year, women spend over $600 million on CAM therapies for menopausal symptoms, such as red clover and black cohosh. In the wake of the Women's Health Initiative, use of CAM products for menopausal symptoms is strongly encouraged by aggressive marketing campaigns, and the level of use is likely to increase. There are several CAM therapies used for menopausal symptoms, including botanicals or herbs (i.e., black cohosh, dong quai, and ginseng) and dietary phytoestrogens (PE). PE products consist of plant-derived nonsteroidal compounds (isoflavones, lignans) with estrogen-like biologic activity. Black cohosh (Actaea racemosa) is one of the most widely used herb for the treatment of menopause symptoms. Use within the United States originated in indigenous Native American cultures and persists today. Several small studies have indicated that black cohosh may decrease menopausal symptoms, including hot flashes. A German Commission recommended the use of black cohosh for menopausal symptoms but indicated that use should be limited to six months. Further work is needed to verify the efficacy of black cohosh in the treatment of menopausal symptoms. Other herbs, such as dong quai (Angelica sinensis), ginseng (Panex ginseng) and red clover (Trifilium pratense) are also used, although their effectiveness for menopause has not yet been thoroughly studied. There are epidemiological studies that have found fewer cardiac events and hot flashes in postmenopausal populations with high soy consumption. A small number of clinical studies have also shown lower blood pressure and cholesterol levels in those with increased soy intake (25 g soy protein/day). However, findings are equivocal regarding effects on hot flash frequency/severity.

NCCAM supports a range of research projects on menopause, including work at several research centers. Ongoing 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 associated with menopause, such as hot flashes, osteoporosis, and cognitive and affective problems. Some of these projects will generate fundamental information on the active ingredients and in vivo characteristics of botanicals used to treat menopausal symptoms. Others will generate clinical

information on their safety and efficacy. 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. Examples of more clinically oriented ongoing research include a study on the impact of phytoestrogens on cognition among menopausal women and an epidemiologic study of the influence of soy consumption on menopause in Japan.

The NCCAM-funded Center for CAM Research in Aging and Women's Health at Columbia University in New York is investigating several therapies hypothesized to effect women's health in menopause. Studies include: macrobiotic diet and flax seed effects on estrogens, phytoestrogens and fibrinolytic factors, dietary phytoestrogens and bone metabolism, and the effects of black cohosh on menopausal hot flashes.

The Center on Botanical Dietary Supplements for Women's Health in Chicago, supported by the Office of Dietary Supplements (ODS) and NCCAM, is studying the clinical safety and efficacy of botanicals used to treat women's health with particular emphasis on therapies for menopause. Projects aim to standardize botanical dietary supplements, to isolate active compounds for structure elucidation, and to determine the mechanism(s) of several botanicals used for women's health (Vitex agnus-castus [VACS], black cohosh and red clover). In addition, Phase I and Phase II clinical trials are underway to determine the efficacy of black cohosh and red clover to decrease the frequency and intensity of hot flashes in healthy menopausal women. Secondary end points will determine (i) the efficacy of black cohosh and red clover for the relief of somatic symptoms (e.g., insomnia, joint pain and fatigue) in healthy menopausal women; (ii) the efficacy of black cohosh and red clover for the relief of sexual dysfunction (e.g., vaginal dryness, pain during sex, libido, difficulty in achieving orgasm); (iii) the longer-term (one year) effects and possible risks associated with the use of black cohosh and red clover; and (iv) the biochemical markers (e.g., lipids, bone turnover, effects on the endometrium) of black cohosh and red clover.

A third ODS/NCCAM-funded Center, the Botanical Center for Age-Related Diseases in Indiana, focuses on characterizing active ingredients in botanicals. The emphasis 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 the prostate, breast and bone, and soy and estrogen interactions on breast and endometrium markers.

Grant Number	PI Name	Project Title
1R21AT001102	SAUTER, EDWARD	The Effect of Black Cohosh Extract on the Human Breast
5R21AT000567	KRIKORIAN, ROBERT	Phytoestrogens and Cognition in Menopause
5F31AT000800	BURDETTE, JOANNA	Cimicifuga racemosa as a serotonin modulator
1F31AT001041	MELBY, MELISSA	Influence of Soy Consumption on Menopause in Japan
1P20AT000856	PRESTWOOD, KAREN	Exploratory Program Grant for Frontier Medicine
1F31AT00804	BOOTH, NANCY	Biological and Cehmical Activity of Trifolium pratense
5P50AT000155	FARNSWORTH, NORMAN	BOTANICAL DIETARY SUPPLEMENTS FOR WOMEN'S HEALTH
5P50AT000090	KRONENBERG, FREDI	CENTER FOR CAM RESEARCH IN AGING
1P50AT00477	WEAVER, CONNIE	BOTANICAL CENTER FOR AGE-RELATED DISEASES

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.

Neither hormone replacement therapy nor vitamin supplements has beneficial effects on coronary blood vessel disease

Coronary artery disease is a leading cause of heart attacks and death. The Women's Angiographic Vitamin and Estrogen (WAVE) Trial followed 423 postmenopausal women between July 1997 and January 2002 in seven clinical centers in the United States and Canada, including the Johns Hopkins Bayview Medical Center, with funding from the NCRR. All women in the study had at least one coronary artery blocked (stenosis). The trial was designed to determine whether hormone replacement therapy (HRT) or antioxidant vitamin supplements, alone or in combination, affected the stenosis. Participants took either 0.625 mg per day of conjugated equine estrogen (plus 2.5 mg per day of medroxyprogesterone acetate for women who had not had a hysterectomy), or matching placebo, and 400 IU of vitamin E twice daily plus 500 mg of vitamin C twice daily, or placebo. After an average of 2.8 years the coronary disease advanced more in the HRT group than in those who took the placebo. There was also a worsening of coronary disease in participants who took the vitamins compared with the placebo, although this did not reach statistical significance. In postmenopausal women with coronary disease, neither HRT nor antioxidant vitamin supplements provide cardiovascular benefit. Instead, a potential for harm was suggested with each treatment.

David D. Waters, MD; Edwin L. Alderman, MD; Judith Hsia, MD; Barbara V. Howard, PhD; Frederick R. Cobb, MD; William J. Rogers, MD; Pamela Ouyang, MD; Paul Thompson, MD; Jean Claude Tardif, MD; Lyall Higginson, MD; Vera Bittner, MD; Michael Steffes, MD, PhD; David J. Gordon, MD, PhD; Michael Proschan, PhD; Naji Younes, PhD; Joel I. Verter, PhD. Effects of Hormone Replacement Therapy and Antioxidant Vitamin Supplements on Coronary Atherosclerosis in Postmenopausal Women. A Randomized Controlled Trial. *JAMA*. 2002;288:2432-2440.

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

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.* 2003;289:323-330.

NCRR MENOPAUSE RESEARCH RELATED GRANTS – FY 2002

GRANT NUMBER	TITLE	PRINCIPAL INVESTIGATOR	INSTITUTION
G12RR003051	ACT 5 III: WOMEN HEALTH: MENOPAUSE & HEALTH IN HISPANIC WOMEN IN PUERTO RICO	ROMAGUERA, JOSEFINA	UNIVERSITY OF PUERTO RICO MED SCIENCES
G12RR013646	P2: ESTROGEN REPLACEMENT THERAPY & NEURON STRUCTURE: ALZHEIMERS	CLAIBORNE, BRENDA J	UNIVERSITY OF TEXAS SAN ANTONIO
K01RR000170	NON HUMAN PRIMATE MODEL OF NATURAL MENOPAUSE CARDIOVASCULAR DIS OSTEOPOROSIS	HONORE, ERIKA K	SOUTHWEST FOUNDATION FOR BIOMEDICAL RES
K23RR016067	WOMEN AT HIGH RISK FOR CAD AFTER MENOPAUSE: BENEFITS OF ERT	CARR, MOLLY C	UNIVERSITY OF WASHINGTON
K23RR016321	POSTMENOPAUSAL HORMONAL REPLACEMENT THERAPY SYMPATHIC NERVE & HYPERTESION	VONGPATANASIN, WANPEN	UNIVERSITY OF TEXAS SW MED CTR/DALLAS
K23RR017043	NEUROBIOLOGICAL EFFECT OF LONG-TERM ESTROGEN REPLACEMENT	SMITH, YOLANDA R	UNIVERSITY OF MICHIGAN AT ANN ARBOR
M01RR000030	HEART DISEASE IN WOMEN: ESTROGEN EFFECTS ON HEMODYNAMICS	SHERWOOD, ANDREW	DUKE UNIVERSITY
M01RR000032	POST MENOPAUSAL HORMONE THERAPY	GOWER, BARBARA	UNIVERSITY OF ALABAMA AT BIRMINGHAM
M01RR000034	IMPACT OF ENZYME-INDUCING ANTIEPILEPTIC DRUGS ON HORMONE REPLACEMENT THERAPY	MCAULEY, JAMES W	OHIO STATE UNIVERSITY
M01RR000036	WASHINGTON UNIVERSITY CLAUDE D. PEPPER OAIC.	HOLLOSZY, JOHN	WASHINGTON UNIVERSITY
M01RR000037	FOLLICLE DEVELOPMENT STUDY	KLEIN, NANCY	UNIVERSITY OF WASHINGTON
M01RR000037	ESTROGENS, BODY FAT AND DYSLIPIDEMIA AT MENOPAUSE	CARR, MOLLY	UNIVERSITY OF WASHINGTON
M01RR000037	SLEEP IN OLDER WOMEN: EFFECTS OF ESTROGEN	MOE, KAREN	UNIVERSITY OF WASHINGTON
M01RR000037	EXERCISE EFFECTS ON HORMONES IN POST-MENOPAUSAL WOMEN	MCTIERNAN, ANNE	UNIVERSITY OF WASHINGTON
M01RR000040	THE EFFECTS OF ESTROGEN AND DHEA SUPPLEMENTATION ON SERUM LIPIDS, & MUSCLE MASS	BARNHART, KURT	UNIVERSITY OF PENNSYLVANIA
M01RR000040	NMR IMAGING AND STEROLOGIC ANALYSIS OF TRABECULAR BONE	WEHRLI, FELIX	UNIVERSITY OF PENNSYLVANIA
M01RR000042	ROLE OF GLUCOSE IN MENOPAUSAL HOT FLASHES	DORMIRE, SHARON L	UNIVERSITY OF MICHIGAN AT ANN ARBOR
M01RR000042	SAFETY OF ESTROGENS IN LUPUS ERYTHEMATOSUS NATIONAL ASSESSMENT (SELENA)	MCCUNE, WILLIAM J	UNIVERSITY OF MICHIGAN AT ANN ARBOR

M01RR000042	EFFECT OF TRANSDERMAL ESTROGEN & ORAL ISOFLAVONE ON SEX HORMONE-BINDING GLOBULIN	LEE, CATHY C	UNIVERSITY OF MICHIGAN AT ANN ARBOR
M01RR000042	THE ROLE OF HYPOTHALAMIC AGING IN MENOPAUSE	REAME, NANCY E	UNIVERSITY OF MICHIGAN AT ANN ARBOR
M01RR000042	AGE AND MENOPAUSE EFFECTS ON INDICATORS OF BONE HEALTH	LUKACS, JANE L	UNIVERSITY OF MICHIGAN AT ANN ARBOR
M01RR000046	WOMEN'S HEALTH INITIATIVE	HEISS, GERARDO	UNIVERSITY OF NORTH CAROLINA CHAPEL HILL
M01RR000047	HORMONE REPLACEMENT THERAPY IN MENOPAUSAL WOMEN WITH EPILEPSY	HARDEN, CYNTHIA L.	WEILL MEDICAL COLLEGE OF CORNELL UNIV
M01RR000048	EPIDEMIOLOGY OF OSTEOPOROSIS IN WOMEN WITH LUPUS - MAMDC PROJECT	RAMSEY-GOLDMAN, ROSALIND	NORTHWESTERN UNIVERSITY
M01RR000051	DHEA, SEX STEROIDS AND COGNITION IN POST-MENOPAUSAL WOMEN	HIRSHMAN, ELLIOT	UNIVERSITY OF COLORADO HLTH SCIENCES CTR
M01RR000051	INFLUENCE OF HORMONE REPLACEMENT THERAPY ON ARTERIAL FUNCTION/STRUCTURE	MOREAU, KERRIE	UNIVERSITY OF COLORADO HLTH SCIENCES CTR
M01RR000051	MODULATION OF WHOLE BODY AND REGIONAL ADIPOSE TISSUE LIPOLYSIS AFTER MENOPAUSE	KOHRT, WENDY	UNIVERSITY OF COLORADO HLTH SCIENCES CTR
M01RR000051	MECHANISMS OF VISCERAL FAT ACCUMULATION IN OLDER WOMEN	GOZANSKY, WENDEE	UNIVERSITY OF COLORADO HLTH SCIENCES CTR
M01RR000051	MODULATION OF VISCERAL FAT BY ESTROGENS AFTER MENOPAUSE	KOHRT, WENDY	UNIVERSITY OF COLORADO HLTH SCIENCES CTR
M01RR000052	EFFECT OF HORMONE REPLACEMENT ON THE PROGRESSION OF ATHEROSCLEROSIS...	OUYANG, PAMELA	JOHNS HOPKINS UNIVERSITY
M01RR000054	SELECTIVE ESTROGEN RECEPTOR MODULATION: EFFECTS IN POST-MENOPAUSAL WOMEN	UDELSON, JAMES	NEW ENGLAND MEDICAL CENTER HOSPITALS
M01RR000056	THE EFFECT OF PHYTOESTROGEN SUPPLEMENTATION ON POST-MENOPAUSAL ENDOMETRIUM	BALK, JUDY	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
M01RR000056	CIRCULATING ANDROGENS LEVELS IN POSTMENOPAUSAL WOMEN W/POLYCYSTIC OVARY SYNDROME	KORYTKOWSKI, MARY	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
M01RR000056	WOMEN'S HEALTH INITIATIVE	KULLER, LEWIS	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
M01RR000056	RANDOMIZED DBL-BLIND...HORMONE REPLACEMENT IN POSTMENOPAUSAL WOMEN W/SLE	MANZI, SUSAN	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
M01RR000056	HORMONE METABOLISM AND BREAST MASSES	MODUGNO, FRANCESMARY	UNIVERSITY OF PITTSBURGH AT PITTSBURGH

M01RR000056	A FUNCTIONALLY BASED APPROACH TO THE TREATMENT OF INCONTINENCE	BORELLO-FRANCE, DIANE	UNIVERSITY OF PITTSBURGH AT PITTSBURGH
M01RR000058	CLINICAL TRIAL AND OBSERVATIONAL STUDY OF THE WOMEN'S HEALTH INITIATIVE	KOTCHEN, JANE	MEDICAL COLLEGE OF WISCONSIN
M01RR000059	THE WOMEN'S HEALTH INITIATIVE	WALLACE, ROBERT B.	UNIVERSITY OF IOWA
M01RR000065	PERIPHERAL VASCULAR ENDOTHELIAL FUNCTION AFTER MENOPAUSE	ARROWOOD, JAMES	VIRGINIA COMMONWEALTH UNIVERSITY
M01RR000065	INSULIN RESISTANCE & CARDIOVASCULAR RISK IN POSTMENOPAUSAL WOMEN WITH PCOS	NESTLER, JOHN E	VIRGINIA COMMONWEALTH UNIVERSITY
M01RR000065	PROGESTERONE ADMINISTRATION ON ENDOTHELIAL FUNCTION IN POSTMENOPAUSAL WOMEN	ARROWOOD, JAMES	VIRGINIA COMMONWEALTH UNIVERSITY
M01RR000073	OVARIAN STEROIDS IN MENOPAUSAL WOMEN WITH ENDOMETRIAL CANCER	NAGAMANI, MANUBAI	UNIVERSITY OF TEXAS MEDICAL BR GALVESTON
M01RR000073	EFFECT OF RALOXIFENE ON INSULIN SENSITIVITY IN NORMAL POSTMENOPAUSAL WOMEN	NAGAMANI, MANUBAI	UNIVERSITY OF TEXAS MEDICAL BR GALVESTON
M01RR000080	SOY PHYTOESTROGEN AND CALCIUM SUPPLEMENTATION ON BONE RESORPTION/FORMATION	HARKNESS, LAURA	CASE WESTERN RESERVE UNIVERSITY
M01RR000095	THE EFFECTS OF 3 DIFFERENT DOSES OF ENTERIC COATED BAYER ASPIRIN ON LEVELS OF	KERINS, DAVID	VANDERBILT UNIVERSITY
M01RR000109	ESTROGEN MODULATION EFFECTS ON CHOLINERGIC FUNCTION IN POST-MENOPAUSAL WOMEN	NEWHOUSE, PAUL A	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE
M01RR000109	EFFECT OF HRT ON CARDIOVASCULAR HEMODYNAMICS IN MENOPAUSAL WOMEN	SITES, CYNTHIA K	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE
M01RR000109	MECHANISM OF MUSCLE PROTEIN LOSS IN MENOPAUSE	MATTHEWS, DWIGHT E	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE
M01RR000109	ESTROGEN AND MOOD AND COGNITION FOLLOWING MONOAMINERGIC DEPLETION	NEWHOUSE, PAUL A	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE
M01RR000109	ESTROGEN AND CHOLINERGIC FUNCTION IN NORMAL POST-MENOPAUSAL WOMEN	NEWHOUSE, PAUL A	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE
M01RR000109	HORMONE REPLACEMENT THERAPY AND METABOLIC CARDIOVASCULAR RISK	SITES, CYNTHIA K	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE
M01RR000109	ENERGY METABOLISM DURING THE MENOPAUSE TRANSITION	MATTHEWS, DWIGHT E	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE
M01RR000109	HRT TO AUGMENT LOSS OF VISCERAL FAT AND IMPROVE INSULIN SENSITIVITY	MATTHEWS, DWIGHT E	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE
M01RR000125	PERIMENOPAUSAL SYMPTOMS	COHEN, SUSAN	YALE UNIVERSITY

	MANAGEMENT WITH ACUPUNCTURE	DSN	
M01RR000188	EFFECTS OF SOY ISOFLAVONES ON NITRIC OXIDE PRODUCTION IN POSTMENOPAUSAL WOMEN	WONG, WILLIAM	BAYLOR COLLEGE OF MEDICINE
M01RR000334	STUDY OF TAMOXIFEN AND RALOXIFENE (STAR) FOR BREAST CANCER PREVENTION	NICHOLS, CRAIG	OREGON HEALTH & SCIENCE UNIVERSITY
M01RR000334	BREAST CANCER SURVIVORS: EXERCISE AND RALOXIFENE	SCHWARTZ, ANNA	OREGON HEALTH & SCIENCE UNIVERSITY
M01RR000400	SOY, PROBIOTICS, AND BREAST CANCER PREVENTION	KURZER, MINDY	UNIVERSITY OF MINNESOTA TWIN CITIES
M01RR000425	CLINICAL TRIAL&OBSERVATIONAL STUDY OF WOMEN'S HEALTH INITIATIVE-WEST	CHLEBOWSKI, ROWAN T	HARBOR-UCLA RESEARCH & EDUC INST
M01RR000585	SEROLOGIC SERBB1 IN HEALTHY WOMEN	BARON, ANDRE T	MAYO CLINIC ROCHESTER
M01RR000585	BONE DENSITY AMONG HISPANIC OLMSTED COUNTY RESIDENTS: A CROSS-SECTIONAL AND LON	RIGGS, B LAWRENCE	MAYO CLINIC ROCHESTER
M01RR000585	MECHANISM OF INCREASED OSTEOCLASTOGENESIS DURING ESTROGEN DEFICIENCY	EGHBALI, GUITI Z	MAYO CLINIC ROCHESTER
M01RR000585	THE ROLE OF PARATHYROID HORMONE (PTH) IN AGE-RELATED CHANGES IN BONE TURNOVER	RIGGS, B LAWRENCE	MAYO CLINIC ROCHESTER
M01RR000633	SIMVASTIN/HRT IN POSTMENOPAUSAL WOMEN WITH NIDDM	GARG, ABHIMANYU	UNIVERSITY OF TEXAS SW MED CTR/DALLAS
M01RR000645	THE FIBRINOLYTIC POTENTIAL OF ESTROGEN IN WOMEN	GIARDINA, ELSA-GRACE V	COLUMBIA UNIVERSITY HEALTH SCIENCES
M01RR000645	RALOXIFENE IN PRIMARY HYPERPARATHYROIDISM	SILVERBERG, SHONNI J	COLUMBIA UNIVERSITY HEALTH SCIENCES
M01RR000645	BLACK COHOSH AND HOT FLASHES	KRONENBERG, FREDI	COLUMBIA UNIVERSITY HEALTH SCIENCES
M01RR000645	THE CHOICE PROJECT: COMPARING HEALTHY OPTIONS IN COOKING AND EATING	BILEZIKIAN, JOHN	COLUMBIA UNIVERSITY HEALTH SCIENCES
M01RR000645	THE EFFECTS OF HORMONE REPLACEMENT THERAPY IN DIABETIC WOMEN	TUCK, CATHERINE	COLUMBIA UNIVERSITY HEALTH SCIENCES
M01RR000645	ALZHEIMER'S DISEASE PREVENTION TRIAL WITH ESTROGEN	SANO, MARY	COLUMBIA UNIVERSITY HEALTH SCIENCES
M01RR000827	GENDER DIFFERENCES IN SUSCEPTIBILITY TO FATTY ACID INDUCED INSULIN RESISTANCE	KRUSZYNSKA, YOLANTA	UNIVERSITY OF CALIFORNIA SAN DIEGO
M01RR000827	HEALTH EFFECTS OF POSTMENOPAUSAL PHYTOESTROGEN USE	KRITZ-SILVERSTE, DONNA	UNIVERSITY OF CALIFORNIA SAN DIEGO
M01RR000827	SOY AND POSTMENOPAUSAL HEALTH IN AGING (SOPHIA)	KRITZ-SILVERSTE, DONNA	UNIVERSITY OF CALIFORNIA SAN

			DIEGO
M01RR000827	HORMONE REPLACEMENT THERAPY AND ADRENERGIC PHYSIOLOGY	MILLS, PAUL J	UNIVERSITY OF CALIFORNIA SAN DIEGO
M01RR000833	MELATONIN TREATMENT FOR SLEEP DISTURBANCES DURING MENOPAUSE	DARKO, DENIS F	SCRIPPS RESEARCH INSTITUTE
M01RR000847	SEX-STEROID CONTROL OF GH FEEDBACK ON EXERCISE	VELDHUIS, JOHANNES D	UNIVERSITY OF VIRGINIA CHARLOTTESVILLE
M01RR000847	EFFECTS OF AGE ON HYPOTHALAMIC-PITUITARY-OVARIAN ACTIVITY IN NORMAL WOMEN	EVANS, WILLIAM S	UNIVERSITY OF VIRGINIA CHARLOTTESVILLE
M01RR000865	PILOT PROJECT TO STUDY HRT, HPA AXIS REACTIVITY AND MEMORY FUNCTION	SEEMAN, TERESA	UNIVERSITY OF CALIFORNIA LOS ANGELES
M01RR001032	THE ROLE OF ESTROGEN ON VASCULAR FUNCTION IN INSULIN RESISTANT WOMEN	GOLDFINE, ALLISON B	BETH ISRAEL DEACONESS MEDICAL CENTER
M01RR001032	HORMONE REPLACEMENT IN MENOPAUSAL WOMEN WITH EPILEPSY	HERZOG, ANDREW G	BETH ISRAEL DEACONESS MEDICAL CENTER
M01RR001066	RALOXIFENE ON BNE MASS & SERUM PROLACTIN LVLS/MENOPAUSAL WM W/HYPERPROLACTINEMIA	KLIBANSKI, ANNE	MASSACHUSETTS GENERAL HOSPITAL
M01RR001066	PITUITARY CONTRIBUTION TO THE DECLINE IN GONADOTROPIN SECRETION WITH AGE	HALL, JANET E	MASSACHUSETTS GENERAL HOSPITAL
M01RR001066	A GNRH ANTAGONIST (NAL-GLU GNRH ANTAGONIST) IN PMW	HALL, JANET E	MASSACHUSETTS GENERAL HOSPITAL
M01RR001346	EFFECT OF JUMPING EXERCISE INTERVENTION BONE MINERAL DENSITY IN POST MENOP WMN	NEWSTEAD, ANN	UNIVERSITY OF TEXAS HLTH SCI CTR SAN ANT
M01RR002558	BUCCAL ESTROGEN IN TOOTHPASTE STUDY	ALI, VASEEM	UNIVERSITY OF TEXAS HLTH SCI CTR HOUSTON
M01RR002558	SAFETY OF ESTROGENS IN LUPUS ERYTHEMATOSUS - NATIONAL ASSESSMENT	FRIEDMAN, ALAN W	UNIVERSITY OF TEXAS HLTH SCI CTR HOUSTON
M01RR002602	EFFECT OF PROGESTOGENS ON BONE AND COGNITION	MUSE, KEN	UNIVERSITY OF KENTUCKY
M01RR002635	ADDITION OF TESTOSTERONE TO HRT ENHANCES QOL AND LIBIDO IN POSTMENOPAUSAL WOMEN	GINSBURG, ELIZABETH S	BRIGHAM AND WOMEN'S HOSPITAL
M01RR002719	EFFECTS OF SEX HORMONE REPLACEMENT THERAPY ON COGNITION & MOOD IN OLDER ADULTS	MAKI, PAULINE	JOHNS HOPKINS UNIVERSITY
M01RR002719	HORMONE REPLACEMENT THERAPY AFTER CORONARY ARTERY BYPASS SURGERY	OUYANG, PAMELA	JOHNS HOPKINS UNIVERSITY
M01RR002719	ESTROGEN/SERMS EFFECTS ON COGNITION AND BRAIN FUNCTION	MAKI, PAULINE	JOHNS HOPKINS UNIVERSITY

M01RR002719	WOMEN'S ANGIOGRAPHIC VITAMINS AND ESTROGEN (WAVE) TRIAL	OUYANG, PAMELA	JOHNS HOPKINS UNIVERSITY
M01RR002719	BLSA: PERIMENOPAUSAL INITIATIVE	BELLANTONI, MICHELE F	JOHNS HOPKINS UNIVERSITY
M01RR003186	WOMEN'S HEALTH INITIATIVE -- UNIVERSITY OF WISCONSIN-MADISON CLINICAL CENTER	ALLEN, CATHERINE I	UNIVERSITY OF WISCONSIN MADISON
M01RR005096	EFFECTS OF ESTROGEN REPLACEMENT IN TYPE 2 DIABETES	FRIDAY, KAREN E.	TULANE UNIVERSITY OF LOUISIANA
M01RR006192	EFFECT OF HORMONE REPLACEMENT THERAPY ON BONE IN OLDER WOMEN	PRESTWOOD, KAREN	UNIVERSITY OF CONNECTICUT SCH OF MED/DNT
M01RR006192	TRANSDERMAL PROGESTERONE ON BONE TURNOVER	RAISZ, LAWRENCE G	UNIVERSITY OF CONNECTICUT SCH OF MED/DNT
M01RR007122	KI-67 LEVELS IN BREAST CORE BIOPSY SPECIMENS FROM POSTMENOPAUSAL WOMEN	VITOLINS, MARA Z	WAKE FOREST UNIVERSITY HEALTH SCIENCES
M01RR007122	WOMEN'S HEALTH INITIATIVE MEMORY STUDY (WHIMS)	VITOLINS, MARA Z	WAKE FOREST UNIVERSITY HEALTH SCIENCES
M01RR007122	POSTMENOPAUSAL HORMONE REPLACEMENT THERAPY AFTER CORONARY BYPASS SURGERY (EAGER)	HERRINGTON, DAVID M	WAKE FOREST UNIVERSITY HEALTH SCIENCES
M01RR007122	VASOMOTOR EFFECT OF HORMONAL REPLACEMENT REGIMENS	HUNDLEY, W GREGORY	WAKE FOREST UNIVERSITY HEALTH SCIENCES
M01RR007122	WOMEN'S HEALTH INITIATIVE (WHI) VANGUARD CLINICAL CENTER TRIAL	BURKE, GREGORY L	WAKE FOREST UNIVERSITY HEALTH SCIENCES
M01RR010284	ALZHEIMER—ESTROGEN	OBISESAN, THOMAS O	HOWARD UNIVERSITY
M01RR010732	EFFECTS OF THE GLYCEMIC INDEX OF FOODS ON CVD RISK IN POST MENOPAUSAL WOMEN	PELKMAN, CHRISTINE L	PENNSYLVANIA STATE UNIV HERSHEY MED CTR
M01RR010732	NUTRITIONAL STUDY IN POST MENOPAUSAL WOMEN	KRIS-ETHERTON, PENNY M	PENNSYLVANIA STATE UNIV HERSHEY MED CTR
M01RR010732	EFFECTS OF THE GLYCEMIC INDEX OF FOODS ON CVD RISK IN POST-MENOPAUSAL WOMEN	PELKMAN, CHRISTINE L	PENNSYLVANIA STATE UNIV HERSHEY MED CTR
M01RR013987	A PHASE I STUDY OF BLACK COHOSH AND RED CLOVER IN HEALTHY MENOPAUSAL WOMEN	SHULMAN, LEE PHILLIP	UNIVERSITY OF ILLINOIS AT CHICAGO
N02RR001132	CLINICAL RESEARCH LRP	GOZANSKY, WENDOLYN S	UNIVERSITY OF COLORADO HEALTH SCI CTR
P20RR015592	KY COBRE: ACTIONS OF ESTRADIOL & SERMS ON COGNITION, MOOD & EFFECT	KELLY, THOMAS	UNIVERSITY OF KENTUCKY
P41RR000862	AMYLOIDOSIS IN RESPONSE TO OVARIECTOMY IN TRANSGENIC MODEL OF ALZHEIMERS DISEASE	DUFF, KAREN	ROCKEFELLER UNIVERSITY
P41RR000954	WEIGHT LOSS & RESISTANCE	JOSEPH, LYNDON	WASHINGTON

	TRAINING ON INSULIN ACTION IN POSTMENOPAUSAL WOMEN	JO	UNIVERSITY
P41RR000954	BONE DENSITY RESPONSE TO ESTROGEN REPLACEMENT IN ELDERLY WOMEN	VILLAREAL, DENNIS T	WASHINGTON UNIVERSITY
P41RR001192	BREAST CANCER DETECTION USING FREQUENCY DOMAIN PHOTON MIGRATION	BUTLER, JOHN A	UNIVERSITY OF CALIFORNIA IRVINE
P41RR011623	MECHANISMS OF RADIATION INDUCED OOCYTE LOSS	TILLY, JONATHAN Z	COLUMBIA UNIVERSITY HEALTH SCIENCES
P51RR000163	OVARIAN STEROID REGULATION OF SEROTONIN NEURAL FUNCTION	BETHEA, CYNTHIA L	OREGON HEALTH & SCIENCE UNIVERSITY
P51RR000163	COGNITION AND ESTROGEN IN MIDDLE-AGED FEMALE MONKEYS	VOYTKO, MARY	OREGON HEALTH & SCIENCE UNIVERSITY
P51RR000165	EFFECTS OF ESTROGENS AND RALOXIFENE ON COGNITION IN AGED FEMALE RHESUS MONKEYS	LACREUSE, AGNES	EMORY UNIVERSITY
P51RR000165	EFFECTS OF ESTROGENS ON COGNITION IN YOUNG FEMALE RHESUS	LACREUSE, AGNES	EMORY UNIVERSITY
P51RR000169	COGNITIVE FUNCTION IN THE AGED MONKEY	RAPP, PETER R	UNIVERSITY OF CALIFORNIA DAVIS
P51RR000169	TREATMENT OF OVARIECTOMIZED-INDUCED BONE LOSS IN CYNOMOLGUS MONKEYS	HENDRICKX, ANDREW G	UNIVERSITY OF CALIFORNIA DAVIS
P51RR000169	ESTROGEN & AGING BRAIN	MORRISON, JOHN	UNIVERSITY OF CALIFORNIA DAVIS
P51RR013986	ESTABLISHMENT OF AN OSTEOPENIC COLONY OF FEMALE BABOONS	CAREY, K DEE	SOUTHWEST FOUNDATION FOR BIOMEDICAL RES
P51RR013986	A PILOT STUDY OF THE PHYSIOLOGY OF THE PERIMENOPAUSE IN BABOONS	HONORE, ERIKA K	SOUTHWEST FOUNDATION FOR BIOMEDICAL RES
P51RR013986	A NONHUMAN PRIMATE MODEL OF NATURAL MENOPAUSE	HONORE, ERIKA K	SOUTHWEST FOUNDATION FOR BIOMEDICAL RES
R01RR014099	NEW TECHNIQUES IN DIAGNOSING OSTEOARTHRITIS: MENOPAUSE	CARLSON, CATHY SUE	UNIVERSITY OF MINNESOTA TWIN CITIES
R24RR016535	THE YUCATAN MICROPIG CARDIOVASCULAR MODEL OF MENOPAUSE: SOY DIET	GOODRICH, JAMES A	MEDICAL UNIVERSITY OF SOUTH CAROLINA

NATIONAL CENTER ON MINORITY HEALTH AND HEALTH DISPARITIES

(NCMHD)

National Center on Minority Health and Health Disparities

The National Center on Minority Health and Health Disparities (NCMHD) promotes minority health and leads the National Institutes of Health (NIH) effort to reduce and ultimately eliminate health disparities. To accomplish these goals, the NCMHD 1) conducts and supports basic, clinical, social, and behavioral research; 2) promotes research infrastructure and training; 3) fosters emerging programs; 4) disseminates information and 5) reaches out to minority and other health disparities communities.

Through its collaborations with the NIH Institutes and Centers, the NCMHD co-funds the following ongoing research projects relevant to menopause.

Grant Number	NIH IC Partner	PI Name	Project Title	Institution	Abstract
AG019360-01A1	National Institute on Aging	Mary Fran R. Sowers	Sleep During the Perimenopause in a Multi-Ethnic Cohort	University of Michigan at Ann Arbor	These Interactive Research Project Grants (IRPG) will characterize the relationship between menopausal characteristics and sleep in a sample of 430 women: 200 Caucasian, 150 African- American, and 80 Chinese. Although sleep disruptions, insomnia and the incidence of sleep disordered breathing increase in mid- life women, little is known about the relationship between menopause and sleep. The impact of vasomotor symptoms and hormone replacement therapy on sleep suggests that the sleep- menopause relationship is not merely a function of age. A greater understanding of the causes of sleep disturbances in mid- life women is important, given the impact of sleep on mental and physical health. Sleep disturbances are associated with a host of negative health outcomes including losses in productivity and quality of life, psychiatric morbidity, immunosuppression, and increased vulnerability to illness and disease. The study aims of this IRPG are to: 1) characterize sleep disturbances in a large, multi-ethnic sample of mid-life women; 2) characterize relationships among menopausal characteristics and sleep disturbances; 3) evaluate the influence of relevant psychobiological factors on the sleep-menopause relationship; and 4) establish baseline data for a future longitudinal study. Four of seven study sites from the ongoing Study of Women's Health Across the Nation (SWAN) will collaborate to recruit a sample of pre- and peri-menopausal women from the SWAN cohort. Once enrolled in the Sleep Study, participants will begin the protocol at the start of a new menstrual cycle. Ambulatory polysomnography will be conducted in participants' homes during days 1-3 of the protocol. Sleep diary, actigraphy, and event monitor recordings of vasomotor symptom data will be collected throughout the cycle. Data will also include five years of Core SWAN study data on menopausal characteristics (bleeding patterns, vasomotor symptoms, hormone levels) and related psychobiological factors. Regression techniques will be used to model relationships among menopausal characteristics, sleep, and related psychobiological factors. The Pittsburgh site will train study personnel in the use of sleep monitoring equipment and will be responsible for processing, scoring, and archiving all sleep data. All sleep study data, as well as relevant data from the Core SWAN study, will be merged and analyzed by the Michigan site. The Chicago and UC Davis PIS will co-chair the Sleep Study Steering Committee.
AG019361-01	National Institute on Aging	Ellen Gold	Sleep During the Perimenopause in a Multi-Ethnic Cohort	University of California, Davis	
AG019362-01	National Institute on Aging	Martica Hall	Sleep During the Perimenopause in a Multi-Ethnic Cohort	University of Pittsburgh at Pittsburgh	
AG019363-01A1	National Institute on Aging	Howard M. Kravitz	Sleep During the Perimenopause in a Multi-Ethnic Cohort	Rush-Presbyterian- St Lukes Medical Center	

HL068492	National Heart, Lung and Blood Institute	Ravi M. Subbiah	Targeted Delivery of Estrogens in Menopause	University of Cincinnati	In postmenopausal women, coronary artery disease (CAD) is the leading cause of death. Estrogen replacement therapy appears to offer considerable protection against CAD in postmenopausal women. However, there is great concern about risk for breast and endometrial cancer after long-term estrogen use in these women. The activation of estrogen receptors and subsequent genomic effects in terms of cell growth appears to play a significant role in estrogen-related carcinogenesis. Our laboratory has been interested in achieving a differential effect of ***estrogens*** by differential delivery to cells. We hypothesize that desired cardioprotective benefits of***estrogens*** (without carcinogenic effects) can be achieved either through a) macrophages targeted for preferential delivery of hydrophobic estrogen acetylated LDL (ac-LDL) complexes to atherosclerotic tissues or b) by conjugating these ***estrogens*** into lipid microspheres or by coating lipoprotein/estrogen complexes with functionalized (Fc) dextran, both of which have been used for preferential uptake by endothelial cells. Phase I will determine a) whether i.v. administered hydrophobic ***estrogens*** will associate with LDL; b) tissue distribution and the feasibility of macrophage-targeted (MT) and endothelium-targeted (ET) liposomal preparation of hydrophobic estrogen derivatives for differential delivery to macrophages or endothelium and c) whether ET and MT are functionally active. Phase II will deal with their in vivo effects on atherogenic indices and suitable lipoprotein-like carriers and enhancers for use as transdermal patch